****

CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" No. RB689522735 US Date of Deposit 2/11/93

I hereby certify that this transmittal together with the application for extension of patent term under 35 U.S.C. 156 referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington D.C. 20231.

MARK LEVY
Name of Person Mailing Paper

Mark Levy
Signature

****

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,219,478
Patentee: Leonardo Marsili,
Vittorio Rossetti, and Carmine Pasqualucci

Issue Date: August 26, 1980 Box:
Patent Term Extension

FOR: RIFAMYCIN COMPOUNDS

TRANSMITTAL OF AN APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

HONORABLE COMMISSIONER OF
PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for a product approved on December 23, 1992.

[X] The application is being mailed by Express Mail under 37 CFR 1.10 and the required Certificate of Mailing appears above. The use of this certificate is intended to insure that the application will be considered as timely filed.

[X] A check in the amount of $1000.00 is attached to cover the cost for the application presented.

Please charge Deposit Account No. 20-0809 for any greater or lesser amount of fees for the application as the Commissioner determines is required by law. This letter is submitted in triplicate.

[X] Three working copies of the APPLICATION FOR EXTENSION OF PATENT TERM and attachments to each are provided for the convenience of the U.S. Patent and Trademark Office.

Respectfully submitted,

Mary Lee
Reg No 27922

Feb 11 1993
Date

Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 with Declaration and attachments thereto

[X] A certified duplicate original APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto

[X] Three working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto

****

CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" Mailing Label No. EB089522735 US Date of Deposit 2/11/93

I hereby certify that this transmittal together with the application for extension of patent term under 35 U.S.C. 156 referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington D.C. 20231.

MARK LEVY
Name of Person Mailing Paper

Mark Levy
Signature

****

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,219,478
Patentee: Leonardo Marsili,
Vittorio Rossetti, and Carmine Pasqualucci

Issue Date: August 26, 1980 Box:
Patent Term Extension

FOR: RIFAMYCIN COMPOUNDS

TRANSMITTAL OF AN APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

HONORABLE COMMISSIONER OF
PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for a product approved on December 23, 1992.

[X] The application is being mailed by Express Mail under 37 CFR 1.10 and the required Certificate of Mailing appears above. The use of this certificate is intended to insure that the application will be considered as timely filed.

[X] A check in the amount of $1000.00 is attached to cover the cost for the application presented.

Please charge Deposit Account No. 20-0809 for any greater or lesser amount of fees for the application as the Commissioner determines is required by law. This letter is submitted in triplicate.

[X] Three working copies of the APPLICATION FOR EXTENSION OF PATENT TERM and attachments to each are provided for the convenience of the U.S. Patent and Trademark Office.

Respectfully submitted,

Mary Lou
Reg No 27922

Feb 11 1993
Date

Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 with Declaration and attachments thereto

[X] A certified duplicate original APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto

[X] Three working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto

#17

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,219,478
Patentee: Leonardo Marsili,
Vittorio Rossetti, and Carmine Pasqualucci

Issue Date: August 26, 1980 Box:
Patent Extension

FOR: RIFAMYCIN COMPOUNDS

REQUEST FOR EXTENSION OF PATENT TERM UNDER
35 U.S.C. 156

HONORABLE COMMISSIONER OF
PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. Sec. 156, FARMITALIA CARLO ERBA S.r.l., MILAN, ITALY, ("F.I.C.E.") assignee of the above-identified patent, through its exclusive licensee ADRIA LABORATORIES a DIVISION of ERBAMONT, INC. hereby requests an extension of the patent term of United States Patent No. 4,219,478. The chain of title to the above-identified patent from the patentees to F.I.C.E. is set out in Exhibit 1, attached hereto, which includes copies of the relevant recorded documents.

100 MG 02/23/93 4219478 2 111 1,000.00 CK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,219,478
Patentee: Leonardo Marsili,
Vittorio Rossetti, and Carmine Pasqualucci

Issue Date: August 26, 1980 Box:
Patent Extension

FOR: RIFAMYCIN COMPOUNDS

DUPLICATE ORIGINAL OF REQUEST
FOR EXTENSION OF PATENT TERM UNDER
35 U.S.C. 156

HONORABLE COMMISSIONER OF
PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

Attached hereto is a duplicate of the application papers for extension of the term of U.S. Patent 4,219,478.

I hereby verify and certify that the attached papers are a duplicate of the original application for extension of the term of U.S. 4,219,478.

Respectfully submitted,

Patricia A. Coburn

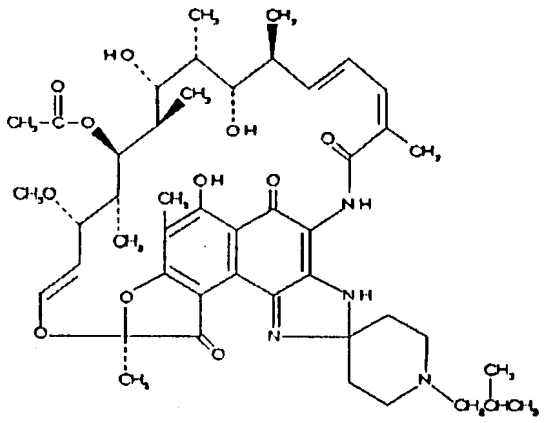
Patricia A. Coburn
Patent Counsel
ADRIA LABORATORIES
P.O. Box 16529
Columbus, Ohio 43216

The following information is submitted in accordance with 35 U.S.C. Sec. 156(d) and 37 CFR 1.740-1.741. For convenience, the formal requirements of 37 CFR 1.740 are specifically set out below and underlined, in accordance with the numerical format set forth therein.

Sec. 1.740(a) An application for extension of patent term must be made in writing to the Commissioner of Patents and Trademarks. A formal application for the extension of patent term shall include:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

The approved product is MYCOBUTIN™ (rifabutin) capsules for oral administration. Rifabutin is an antimycobacterial agent and is a semisynthetic ansamycin antibiotic derived from rifamycin S. Chemically, rifabutin is 1',4-didehydro-1-deoxy-1,4-dihydro-5'-(2-methylpropyl)-1-oxorifamycin XIV (Chemical Abstracts Service, 9th Collective Index) or (9S,12E,14S,15R,16S,17R,18R,19R,20S,21S,22E,24Z)-6,16,18,20-tetrahydro-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-spiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2H-furo[2',3':7,8]napth[1,2-d]imidazole-2,4'-piperidine]-5,10,26-(3H,9H)-trione-16-acetate. The structural formula for rifabutin is as follows:



Rifabutin has a molecular formula of $C_{46}H_{62}N_4O_{11}$ and a molecular weight of 847.02.

The MYCOBUTIN™ brand of rifabutin is available as a capsule for oral administration containing 150 mg of rifabutin per capsule and the following inactive ingredients: microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 507 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. Sec. 301 et seq., and 21 CFR Part 314, which establishes regulations for the submission and approval of new drug applications ("NDAs").

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

MYCOBUTIN™ (rifabutin) capsules was approved by the Food and Drug Administration (FDA") for commercial marketing pursuant to Section 507 of the FFDCA on December 23, 1992; see Exhibit 2 attached hereto.

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and

Cosmetic Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved.

The only active ingredient in MYCOBUTIN™ is rifabutin which has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act. See the copy of the product information insert, Exhibit 3, attached hereto and paragraph (1) hereinabove for additional information on rifabutin.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to Sec. 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on December 23, 1992, and the last day within the sixty day period permitted for submission of an application for extension of the patent is February 20, 1993. This application is being filed on FEB 11, 1993 and, therefor, it has been timely submitted.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, and the date of issue:

U.S. Patent 4,219,478

Inventors: Leonardo Marsili, Vittorio Rossetti and Carmine Pasqualucci

Issue Date: August 26, 1980

Expiration Date: April 25, 1995 (see paragraph 8 below)

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings.

A copy of the subject patent is attached as Exhibit 4.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

Attached as Exhibit 5 is a copy of a Terminal Disclaimer dated January 8, 1979, disclaiming the terminal part of U.S. 4,219,478 (the patent granted on application serial number 913,107 filed June 6, 1978) which would extend beyond the expiration date of U.S. 4,086,225 which date is April 25, 1995.

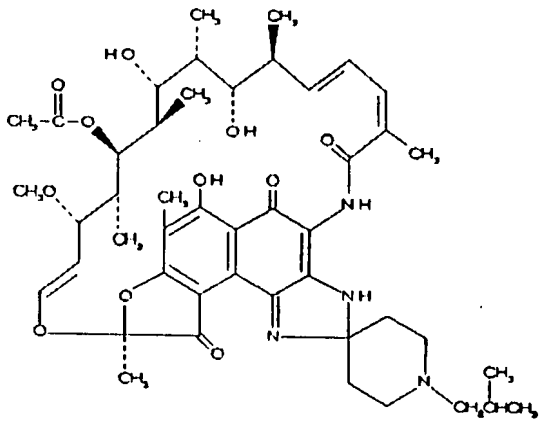
A copy of a Certificate of Correction dated April 14, 1981 is attached as Exhibit 6.

Since the subject patent issued on an application filed prior to December 12, 1980, it is exempt from payment of maintenance fees (35 U.S.C. Sec. 41(b)). No request for re-examination has been filed.

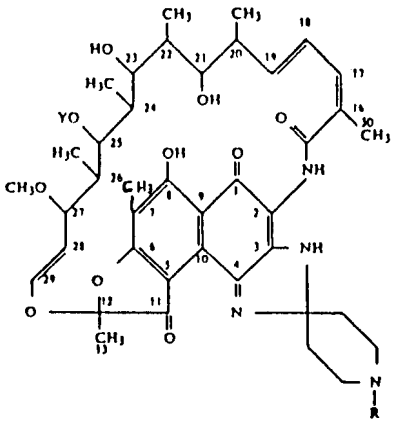
(9) A statement beginning on a new page that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

Claims 1, 2 and 4 of U.S. 4,219,478 are generic compound claims which cover the active ingredient of the approved product.

The active ingredient of the approved product is rifabutin which has the following chemical structure:



The structural formula of the compounds claimed in Claim 1 of U.S. 4,219,478 as corrected by the Certificate of Correction (Exhibit 6) is the following:



wherein the group "R" can be a branched alkyl having from 4 to 8 carbon atoms, and the group "Y" can be $-COCH_3$. As shown by the formula for rifabutin, it is covered by Claim 1 when the group "R" is a branched alkyl having four carbon atoms (i.e., isobutyl), and when the group "Y" is $-COCH_3$.

Each of Claims 2 and 4 are dependent on Claim 1, and each further limits the definition of the group "R". In Claim 2 "R" is limited to a linear or branched alkyl having 4 or 5 carbon atoms. In Claim 4 "R" is limited to a branched alkyl having 4 to 8 carbon atoms. In rifabutin the "R" group is a branched alkyl having 4 carbon atoms (i.e., isobutyl) and therefore, each of Claims 2 and 4 covers the active ingredient of the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. Sec. 156 (g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(i) For a patent that claims a human drug product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number; and the date on which the NDA was approved.

On February 17, 1986, Adria Laboratories submitted to the Food and Drug Administration ("FDA") a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for rifabutin. This submission constituted a pre-IND submission. The remainder of the information to complete the IND was submitted on April 7, 1986 at which time a request for a waiver of the usual 30 day delay was made. On April 18, 1986, waiver of the 30 day delay was granted. The IND was assigned number 27,934. These facts are confirmed in letters from the FDA dated February 24, 1986, April 7, 1986, and June 2, 1986, copies of which are attached as Exhibit 7. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as April 18, 1986.

The IND was expanded and ultimately divided resulting in the establishment of a second IND for rifabutin in January of 1987. The second IND was given the number 29,607. A copy of a letter dated January 8, 1987 and of a letter dated January 14, 1987 each to the FDA substantiating the creation of the second

IND are attached as Exhibit 8. A new drug application (NDA), was submitted under Section 507 of the Federal Food, Drug, and Cosmetic Act (FFDCA) in sections on October 3, 1991, November 21, 1991, and January 16, 1992. The submission made on January 16, 1992 constituted completion of the NDA submission. A copy of the cover letter for the January 16, 1992 submission is attached as Exhibit 9. This letter identifies the submission as NDA 50-689. This NDA was approved on December 23, 1992. Attached as Exhibit 2 is a copy of a letter dated December 23, 1992, from FDA to Adria Laboratories approving the NDA for Mycobutin™ (rifabutin) capsules for oral administration for the prevention of disseminated mycobacterium avium complex (MAC) disease in patients with advanced HIV infection.

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. 156(g)(1), December 23, 1992, is the date of the first approval by the F.D.A. of the approved product.

(11) A brief description beginning on a new page of the significant activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described in item (10) above, Adria Laboratories submitted an IND for rifabutin on April 18, 1986, and, in close consultation with FDA, subsequently conducted clinical studies under this IND and a second IND established in January of 1987. These studies were used to support the new drug application submitted by Adria on January 16, 1992. Subsequent to the submission of this NDA, Adria had numerous contacts and meetings with the FDA with respect to the application. The description set forth in Exhibit 10 of the activities undertaken by Adria with respect to rifabutin during the regulatory review period is illustrative of a diligent pursuit of FDA approval.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. Sec. 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. Sec. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements has been satisfied:

(1) The term of U.S. Patent No. 4,219,478, as set by a terminal disclaimer, expires on April 25, 1995. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by Adria Laboratories, a Division of Erbamont, Inc. as exclusive licensee and agent for FARMITALIA CARLO ERBA S.r.l. Exhibit 11 is a copy of the letter dated March 6, 1986 appointing Adria Laboratories as agent for FARMITALIA CARLO ERBA. This application complies with the provisions of Sec. 35 U.S.C. Sec. 156(d) in that it is submitted within the sixty-day period beginning on the date the product received permission for marketing under the Federal Food, Drug and Cosmetic Act, i.e., December 23, 1992, and contains the information required under 35 U.S.C. Sec. 156(d).

(4) As evidenced by the December 23, 1992 letter from the FDA, Exhibit 2, the approved product was subject to a regulatory review period under Section 507 of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of MYCOBUTIN™ after regulatory review under Section 507 is the first permitted commercial marketing of rifabutin. This is confirmed by the absence of any approved new drug application under which rifabutin could be commercially marketed prior to December 23, 1992.

(b) Statement as to length of extension claimed:

The term of Patent No. 4,219,478 should be extended by 3.81 years. The term of extension was determined as follows

using the Patent and Trademark Office form for "Calculation of Length of Patent Term Extension for a Human Drug Product":

1.	The number of days for the testing phase as defined in 37 C.F.R. 1.7775(c)(1).	2100
2.	The number of days for the approval phase as defined in 37 C.F.R. 1.775(c)(2).	342
3.	Total of line 1 and line 2.	2442
4.	The number of days of the period of line 2 which occurred prior to the issue date of the patent.	0
5.	The number of days of the period of line 2 during which the Applicant failed to act with due diligence as defined in 37 C.F.R. 1.775(d)(1)(ii).	0
6.	Total of line 5 and line 6.	0
7.	Total of line 3 less the amount of line 6.	2442
8.	The number of days of the period of line 1 which occurred prior to the issue date of the patent.	0
9.	The number of days of the period of line 1 during which the Applicant failed to act with due diligence as defined in 37 C.F.R. 1.775(d)(1)(ii).	0
10.	The total of line 8 and line 9.	0
11.	Total of line 7 less the amount of line 10.	2442
12.	The number of days from line 1.	2100
13.	The number of days from line 10.	0
14.	The total from line 12 less the amount of line 13.	2100
15.	One half of line 14.	1050
16.	The total from line 11 less the amount from line 15.	1392
17.	The original expiration date of the patent.	April 25, 1995
18.	The expiration date of the patent	

	if extended by the number of days on line 16. [Note that the year 1996 is a leap year.]	February 15, 1999
19.	Date of the FDA final approval.	December 23, 1992
20.	Limitation set forth in 37 C.F.R. 1.775(d)(3).	14 years
21.	14 years added to the date on line 19 gives a revised date of	December 23, 2008
22.	Earlier of the dates of line 18 or line 21	February 15, 1999
23.	Original expiration date of patent	April 25, 1995
24.	The patent issued prior to 09/24/84 and no request for exemption as defined in 37 C.F.R. 1.775(d)(6)(i) was filed prior to 09/24/84.	5 years
25.	The number of years on line 24 added to the date on line 23.	April 25, 2000
26.	The earlier of the dates appearing on line 22 or line 25.	February 15, 1999
27.	The original expiration date of the patent.	April 25, 1995
28.	The number of days by which line 26 and line 27 differ. [Note that the year 1996 is a leap year.]	1392

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (see Sec. 1.765).

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension. Accordingly, applicant believes all such material information has been set forth hereinabove and in the attached Exhibits 1 to 11.

(14) The prescribed fee for receiving and acting upon the application for extension (see Sec. 1.20(n)).

A check in the amount of $1000.00 is enclosed with this application. Authorization is given to charge any greater or lesser amount due for the application to Deposit Account No. 20-0809.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence are to be directed is:

Mark P. Levy, Esq.
Thompson, Hine & Flory
2000 Courthouse Plaza N.E.
P.O. Box 8801
Dayton, OH 45401-8801

(16) A certified duplicate of these application papers is submitted herewith.

(17) An oath or declaration as set forth in paragraph (b) of 37 C.F.R. 1.741.

DECLARATION

I, Patricia A. Coburn, represent that I am authorized to obligate FARMITALIA CARLO E.R.B.A. S.r.l., Milan, Italy, the owner of record of U.S. Patent 4,219,478 ("the '478 Patent"), which through ADRIA, its exclusive licensee, has applied for an extension of the term of the '478 Patent; I declare that I have reviewed and understand the contents of this application for extension of the '478 Patent which is being submitted pursuant to 37 CFR 1.741; I believe that the '478 Patent is subject to extension under 35 U.S.C. 156 and in accordance with 37 CFR 1.710; I believe that the length of extension claimed is fully justified under 35 U.S.C. 156 and the applicable regulations; and, I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may

jeopardize the validity of this application and any extension of the '478 Patent.

Date: February 2, 1993

ADRIA LABORATORIES, DIVISION
OF ERBAMONT, INC.

By: Patricia A. Coburn
Patricia A. Coburn
Reg. No. 28,594

Exhibit 1

Chain of Title

U.S. Patent 4,219,478

1. Assignment, Leonardo Marsili, Vittorio Rossetti and Carmine Pasqualucci to ARCHIFAR Laboratori Chimico Farmacologici S.p.A.

Reel: 3733 Frame: 169

Date of recording: February 26, 1980

2. Assignment, ARCHIFAR to FARMITALIA CARLO ERBA S.p.A. ("FARMITALIA S.p.A.").

Reel: 3905 Frame: 979

Date of recording: September 9, 1981

3. Assignment, FARMITALIA S.p.A. to FARMITALIA CARLO ERBA S.r.l.

Reel: 5060 Frame: 0892

Date of recording: March 28, 1989

See fourth page, the fifth patent number listed.

Assignment Of Application

WHEREAS, I, (WE) Leonardo Marsili, Vittorio Rossetti, and Carmine Pasqualucci, of Milano 2 - Segrate - Milan, Italy, Viale Gavazzi, 52 - Melzo, Milan, Italy, and Via Crimea, 23 - Milan, Italy, respectively, have invented certain new and useful improvements in: RIFAMYCIN COMPOUNDS, for which an application for Letters Patent was executed on July 3, 1979, and

WHEREAS, ARCHIFAR Laboratori Chimico Farmacologici S.p.A. (hereinafter referred to as "ASSIGNEE") having a place of business at: Corso Verona 165, Rovereto, Italy, is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent that may be granted therefor in the United States and its territorial possessions and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I (WE), by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

I, (WE) hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my (our) entire right, title and interest in and to the same, for the sole use and behoof of the said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me (us) had this Assignment and sale not been made.

Further, I (WE) agree, that I (WE) will communicate to said ASSIGNEE or its (his) representatives any facts known to me (us) respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors, and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

EXECUTED AT: _____

Date: July 3, 1979 — Leonardo Marsili (Signature of Inventor) Leonardo Marsili

Date: July 3,1979 — Vittorio Rossetti (Signature of Inventor) Vittorio Rossetti

Date: _____ — (Signature of Inventor) Carmine Pasqualucci

Date: July 3, 1979 — Carmine Pasqualucci (Signature of Inventor)

Date: _____ — (Signature of Inventor)

OBLON, FISHER, SPIVAK, MCCLELLAND & MAIER
PATENT ATTORNEYS
1755 S. JEFFERSON DAVIS HIGHWAY
CRYSTAL SQUARE - SUITE 400
ARLINGTON, VIRGINIA 22202

2/

ASSIGNMENT OF PATENTS

WHEREAS, We ARCHIFAR LABORATORI CHIMICO FARMACOLOGICI S.p.A. of Corso Verona 165, 38068 Rovereto (Trento) Italy are the assignegs and owners of the U.S. Letters Patents nos. 4017481, 4086225, 4116957, 4124585, 4124586, 4164499, 4165317, 4175077. 4217276, 4217278, 4219478 and 4226765, and

WHEREAS, FARMITALIA CARLO ERBA S.p.A. (hereinafter referred to as "ASSIGNEE") having a place of business at Via Imbonati 24, 20159 Milan - Italy are desirous of acquiring the entire right, title and interest in and to said Letters Patents granted in the United States and its territorial possessions ;

NOW, THEREFORE, in consideration of the sum of one thousand eight hundred and fifty dollars ($. 1850), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, WE by these presents do sell, assign and transfer into said ASSIGNEE, the entire right, title and interest in and to all said Letters Patents granted in the United States and its territorial possessions and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

WE hereby authorize and request the Patent Office Officials in the United States and its territorial possessions to register the assignment all of said Letters Patents to said ASSIGNEE as the assignee of our entire right, title and interest in and to the same, for the sole use and behoof of the said ASSIGNEE, its successors and assigns, to the full end of the term for which said Letters Patents are granted.

Further, WE agree, that WE will communicate to said ASSIGNEE or its representatives any facts known to us respecting said patents, and testify in any legal proceeding, sign all lawful papers, which may be required for recording this Assignment and, generally do everything possible to aid said ASSIGNEE, its successors, and assigns, to obtain and enforce proper protection for said patents in the United States and its territorial possessions.

Roberto Sabbioneda
President - Managing Director

EXECUTED AT : Milan, Italy

Date : 29 June 1981

COMMISSIONER OF PATENTS

against 694,589, Pat. # 4,086,225

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
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TO: OBLON, FISHER, SPIVAK, MC CLELLAND & MAIER
STE. 400, 1755 S. JEFF. DAVIS HWY.
ARLINGTON, VA. 22202

JAN 2 5 1991

OBLON, SPIVAK, McCLELLAND MAIER & NEUSTADT, P.C.

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 FARMITALIA CARLO ERBA S.P.A. DOC DATE: 00/00/00

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DIGEST: CHANGE OF NAME - ADDITIONAL PROPERTIES MAY SUBSEQUENTLY BE INDEXED AGAINST THE ORIGINAL DOCUMENT. THE PAPER REQUESTING SUCH INDEXING MUST ADEQUATELY IDENTIFY ALL SUCH PROPERTIES AND MUST INDICATE THE REEL AND FRAME NUMBER ON WHICH THE ORIGINAL DOCUMENT IS RECORDED.
JULY 20, 1988 ITALY

ASSIGNEE: 501 FARMITALIA CARLO ERBA S.R.L.

SERIAL NUMBER	6-621681	FILING DATE	06/18/84
PATENT NUMBER	4,563,444	ISSUE DATE	01/07/86
SERIAL NUMBER	6-638494	FILING DATE	08/07/84
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SERIAL NUMBER	5-578820	FILING DATE	05/19/75
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PATENT NUMBER	4,675,311	ISSUE DATE	06/23/87

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Patent and Trademark Office
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Washington, D.C. 20231

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	PATENT NUMBER	4,293,705	ISSUE DATE	10/06/81

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SERIAL NUMBER	7-049987	FILING DATE	05/15/87

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PATENT NUMBER	4,840,943	ISSUE DATE	06/20/89
SERIAL NUMBER	7-065597	FILING DATE	06/23/87
PATENT NUMBER	4,843,073	ISSUE DATE	06/27/89
SERIAL NUMBER	7-071079	FILING DATE	07/08/87
PATENT NUMBER		ISSUE DATE	00/00/00
SERIAL NUMBER	6-941348	FILING DATE	12/15/86
PATENT NUMBER	4,808,578	ISSUE DATE	02/28/89
SERIAL NUMBER	6-133035	FILING DATE	03/24/80
PATENT NUMBER	4,312,373	ISSUE DATE	01/26/82

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
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Washington, D.C. 20231

SERIAL NUMBER	6-123855	FILING DATE	02/22/80
PATENT NUMBER	4,277,471	ISSUE DATE	07/07/81
SERIAL NUMBER	6-064653	FILING DATE	08/08/79
PATENT NUMBER	4,228,177	ISSUE DATE	10/14/80
SERIAL NUMBER	6-887438	FILING DATE	07/21/86
PATENT NUMBER	4,771,043	ISSUE DATE	09/13/88
SERIAL NUMBER	6-912070	FILING DATE	09/26/86
PATENT NUMBER	4,749,693	ISSUE DATE	06/07/88
SERIAL NUMBER	6-133043	FILING DATE	03/24/80
PATENT NUMBER	4,304,262	ISSUE DATE	12/08/81
SERIAL NUMBER	7-023390	FILING DATE	03/09/87
PATENT NUMBER	4,942,155	ISSUE DATE	07/17/90
SERIAL NUMBER	7-052380	FILING DATE	05/21/87
PATENT NUMBER	4,785,001	ISSUE DATE	11/15/88
SERIAL NUMBER	6-879886	FILING DATE	06/30/86
PATENT NUMBER	4,786,281	ISSUE DATE	11/22/88
SERIAL NUMBER	6-902873	FILING DATE	09/02/86
PATENT NUMBER	4,769,483	ISSUE DATE	09/06/88
SERIAL NUMBER	6-022247	FILING DATE	00/00/00
PATENT NUMBER		ISSUE DATE	00/00/00
SERIAL NUMBER	6-849388	FILING DATE	04/08/86
PATENT NUMBER	4,837,215	ISSUE DATE	06/06/89
SERIAL NUMBER	6-866713	FILING DATE	05/27/86
PATENT NUMBER		ISSUE DATE	00/00/00
SERIAL NUMBER	6-945866	FILING DATE	12/23/86
PATENT NUMBER		ISSUE DATE	00/00/00
SERIAL NUMBER	7-064708	FILING DATE	06/22/87
PATENT NUMBER	4,784,803	ISSUE DATE	11/15/88
SERIAL NUMBER	7-075776	FILING DATE	07/20/87
PATENT NUMBER	4,787,429	ISSUE DATE	11/29/88
SERIAL NUMBER	0-000000	FILING DATE	00/00/00
PATENT NUMBER	3,792,032	ISSUE DATE	00/00/00
SERIAL NUMBER	5-560104	FILING DATE	00/00/00
PATENT NUMBER	4,058,519	ISSUE DATE	00/00/00

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SERIAL NUMBER	5-823581	FILING DATE	08/11/77
PATENT NUMBER	4,098,798	ISSUE DATE	07/04/78
SERIAL NUMBER	7-009073	FILING DATE	01/27/87
PATENT NUMBER		ISSUE DATE	00/00/00
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PATENT NUMBER	4,271,160	ISSUE DATE	06/02/81
SERIAL NUMBER	6-321628	FILING DATE	11/16/81
PATENT NUMBER	4,406,901	ISSUE DATE	09/27/83
SERIAL NUMBER	6-188620	FILING DATE	09/19/80
PATENT NUMBER	4,321,381	ISSUE DATE	03/23/82
SERIAL NUMBER	6-780255	FILING DATE	09/26/85
PATENT NUMBER		ISSUE DATE	00/00/00
SERIAL NUMBER	7-009550	FILING DATE	02/02/87
PATENT NUMBER	4,861,870	ISSUE DATE	08/29/89
SERIAL NUMBER	7-133043	FILING DATE	10/29/87
PATENT NUMBER	4,895,836	ISSUE DATE	01/23/90
SERIAL NUMBER	7-022247	FILING DATE	03/05/87
PATENT NUMBER	4,886,793	ISSUE DATE	12/12/89
SERIAL NUMBER	7-071584	FILING DATE	07/07/87
PATENT NUMBER		ISSUE DATE	00/00/00
SERIAL NUMBER	6-882364	FILING DATE	07/07/86
PATENT NUMBER	4,808,616	ISSUE DATE	02/28/89
SERIAL NUMBER	7-107050	FILING DATE	10/13/87
PATENT NUMBER		ISSUE DATE	00/00/00
SERIAL NUMBER	6-742859	FILING DATE	06/10/85
PATENT NUMBER	4,623,643	ISSUE DATE	11/18/86
SERIAL NUMBER	7-106809	FILING DATE	10/13/87
PATENT NUMBER		ISSUE DATE	00/00/00

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-689

DEC 23 1992

Larry R. Versteegh, Ph.D.
Senior Vice President,
Regulatory and Scientific Affairs
Adria Laboratories
P.O. Box 16529
Columbus, OH 43216

Dear Dr. Versteegh:

Reference is made to your New Drug Application dated January 16, 1992, submitted pursuant to section 507(b) of the Federal Food, Drug and Cosmetic Act for Mycobutin™ (rifabutin capsules).

We also acknowledge receipt of your additional communications dated as follows:

March 17, 1992
March 23, 1992 (2)
March 25, 1992
March 30, 1992
March 31, 1992
April 6, 1992
April 8, 1992
April 14, 1992
April 15, 1992
April 16, 1992 (2)
April 24, 1992 (2)
April 28, 1992
April 29, 1992
April 30, 1992
May 1, 1992
May 5, 1992
May 6, 1992
May 7, 1992
May 12, 1992 (2)
May 13, 1992 (2)
May 14, 1992 (2)
May 15, 1992 (2)
May 19, 1992
May 21, 1992 (2)
May 26, 1992
May 27, 1992
June 1, 1992
June 24, 1992 (2)
July 1, 1992
July 2, 1992
July 14, 1992
August 5, 1992
August 13, 1992
August 17, 1992
August 18, 1992 (3)
August 19, 1992 (3)
August 20, 1992
August 21, 1992
September 2, 1992 (2)
September 9, 1992
September 10, 1992
September 15, 1992
September 17, 1992
October 1, 1992 (2)
October 12, 1992
October 15, 1992 (2)
November 4, 1992
November 9, 1992
November 11, 1992
November 16, 1992
November 18, 1992
November 19, 1992
November 20, 1992 (2)
November 25, 1992
December 4, 1992
December 9, 1992
December 10, 1992
December 14, 1992
December 15, 1992
December 17, 1992
December 23, 1992

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated December 23, 1992. Accordingly, the application, with these

labeling revisions, is approved, effective on the date of this letter.

These revisions are terms of the NDA approval. Marketing the product before making, exactly as agreed to, the revisions in the product's labeling may render the product misbranded and an unapproved drug.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 50-689". Approval of the submission by FDA is not required before the labeling is used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Please submit one market package when available.

We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81.

Sincerely yours,

James Bilstad, M.D.
Director
Office Drug Evaluation II
Center for Drug Evaluation
and Research
Food and Drug Administration

(3)

Adrtd®

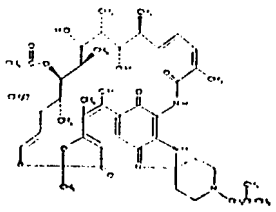
MYCOBUTIN™
(rifabutin capsules)

0570012292

DESCRIPTION

MYCOBUTIN™ is the brand name for the antimycobacterial agent rifabutin. It is a semisynthetic ansamycin antibiotic derived from rifamycin S. MYCOBUTIN capsules for oral administration contain 150 mg of rifabutin per capsule, along with the inactive ingredients microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

The chemical name for rifabutin is 1',4-didehydro-1-deoxy-1,4-dihydro-5'-(2-methylpropyl)-1-oxorifamycin XIV (Chemical Abstracts Service, 9th Collective Index) or (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-tetrahydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-spiro [9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2',3':7,8]naphth[1,2-*d*]imidazole-2,4'-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate. Rifabutin has a molecular formula of $C_{46}H_{62}N_4O_{11}$, a molecular weight of 847.02 and the following structure:



Rifabutin is a red violet powder soluble in chloroform and methanol, sparingly soluble in ethanol, and very slightly soluble in water (0.19 mg/mL). Its log P value (the base 10 logarithm of the partition coefficient between n-octanol and water) is 3.2 (n-octanol/water).

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following a single oral dose of 300 mg to nine healthy adult volunteers, MYCOBUTIN was readily absorbed from the gastrointestinal tract with mean (±SD) peak plasma levels (C_{max}) of 375 (±267) ng/mL (range: 141 to 1033 ng/mL) attained in 3.3 (±0.9) hours (T_{max} range: 2 to 4 hours). Plasma concentrations post-C_{max} declined in an apparent biphasic manner. Kinetic dose-proportionality has been established over the 300 to 600 mg dose range in nine healthy adult volunteers (crossover design) and in 16 early symptomatic human immunodeficiency virus (HIV)-positive patients over a 300 to 900 mg dose range. Rifabutin was slowly eliminated from plasma in seven healthy adult volunteers, presumably because of *distribution-limited elimination*, with a mean terminal half-life of 45 (±17) hours (range: 16 to 69 hours). Although the systemic levels of rifabutin following multiple dosing decreased by 38%, its terminal half-life remained unchanged. Rifabutin, due to its high lipophilicity, demonstrates a high propensity for distribution and intracellular tissue uptake. Estimates of apparent steady-state distribution volume (9.3 ± 1.5 L/kg) in five HIV-positive patients, following I.V. dosing, exceed total body water by approximately 15-fold. Substantially higher intracellular tissue levels than those seen in plasma have been observed in both rat and man. The lung to plasma concentration ratio, obtained at 12 hours, was found to be approximately 6.5 in four surgical patients administered an oral dose. Mean rifabutin steady-state trough levels ($C_{p\text{-}min}$'s; 24-hour post-dose) ranged from 50 to 65 ng/mL in HIV-positive patients and in healthy adult volunteers. About 85% of the drug is bound in a concentration-independent manner to plasma proteins over a concentration range of 0.05 to 1 µg/mL. Binding does not appear to be influenced by renal or hepatic dysfunction.

Mean systemic clearance (CL_s/F) in healthy adult volunteers following a single oral dose was 0.69 (±0.32) L/hr/kg (range: 0.46 to 1.34 L/hr/kg). Renal and biliary clearance of unchanged drug each contribute approximately 5% to CL_s/F. About 30% of the dose is excreted in the feces. A mass-balance study in three healthy adult volunteers with ^{14}C-labeled drug has shown that 53% of the oral dose was excreted in the urine, primarily as metabolites. Of the five metabolites that have been identified, 25-O-desacetyl and 31-hydroxy are the most predominant, and show a plasma metabolite:parent area under the curve ratio of 0.10 and 0.07, respectively. The former has an activity equal to the parent drug and contributes up to 10% to the total antimicrobial activity.

Absolute bioavailability assessed in five HIV-positive patients, who received both oral and I.V. doses, averaged 20%. Total recovery of radioactivity in the urine indicates that at least 53% of the orally administered rifabutin dose is absorbed from the G.I. tract. The bioavailability of rifabutin from the capsule dosage form, relative to a solution, was 85% in 12 healthy adult volunteers. High-fat meals slow the rate without influencing the extent of absorption from the capsule dosage form. The overall pharmacokinetics of MYCOBUTIN are modified only slightly by alterations in hepatic function or age. MYCOBUTIN steady-state kinetics in early symptomatic HIV-positive patients are similar to healthy volunteers. Compared to healthy volunteers, steady-state kinetics of MYCOBUTIN are more variable in elderly patients (>70 years) and in symptomatic HIV-positive patients. Somewhat reduced drug distribution and faster elimination of rifabutin in patients with compromised renal function may result in decreased drug concentrations. The clinical implications of this are unknown.

No rifabutin disposition information is currently available in children or adolescents under 18 years of age.

Microbiology

Mechanism of Action

Rifabutin inhibits DNA-dependent RNA polymerase in susceptible strains of *Escherichia coli* and *Bacillus subtilis* but not in mammalian cells. In resistant strains of *E. coli*, rifabutin, like rifampin, did not inhibit this enzyme. It is not known whether rifabutin inhibits DNA-dependent RNA polymerase in *Mycobacterium avium* or in *M. intracellulare* which comprise *M. avium* complex (MAC).

Susceptibility Testing

In vitro susceptibility testing methods and diagnostic products used for determining minimum inhibitory concentration (MIC) values against *M. avium* complex (MAC) organisms have not been standardized. Breakpoints to determine whether clinical isolates of MAC and other mycobacterial species are susceptible or resistant to rifabutin have not been established.

In Vitro Studies

Rifabutin has demonstrated *in vitro* activity against *M. avium* complex (MAC) organisms isolated from both HIV-positive and HIV-negative people. While gene probe techniques may be used to identify these two organisms, many reported studies did not distinguish between these two species. The vast majority of isolates from MAC-infected, HIV-positive people are *M. avium*, whereas in HIV-negative people, about 40% of the MAC isolates are *M. intracellulare*.

Various *in vitro* methodologies employing broth or solid media, with and without polysorbate 80 (Tween 80), have been used to determine rifabutin MIC values for mycobacterial species. In general, MIC values determined in broth are several fold lower than that observed with methods employing solid media. Utilization of Tween 80 in these assays has been shown to further lower MIC values. However, MIC values were substantially higher for egg based compared to agar based solid media.

Rifabutin activity against 211 MAC isolates from HIV-positive people was evaluated *in vitro* utilizing a radiometric broth and an agar dilution method. Results showed that 74% and 77% of these isolates had MIC_{99} values of ≤0.25 µg/mL and ≤1.0 µg/mL, respectively, when evaluated by these two methods. Rifabutin was also shown to be active against phagocytized, *M. avium* complex in a mouse macrophage cell culture model.

Rifabutin has *in vitro* activity against many strains of *Mycobacterium tuberculosis*. In one study, utilizing the radiometric broth method, each of 17 and 20 rifampin-naive clinical isolates tested from the United States and Taiwan, respectively, were shown to be susceptible to rifabutin concentrations of ≤0.125 µg/mL.

Cross-resistance between rifampin and rifabutin is commonly observed with *M. tuberculosis* and *M. avium* complex isolates. Isolates of *M. tuberculosis* resistant to rifampin are likely to be resistant to rifabutin. Rifampicin and rifabutin MIC_{99} values against 523 isolates of *M. avium* complex were determined utilizing the agar dilution method (Ref. Heifets, Leonid B. and Iseman, Michael D. 1985. Determination of *in vitro* susceptibility of Mycobacteria to Ansamycin. Am. Rev. Respir. Dis. *132* (3):710-711).

SUSCEPTIBILITY OF *M. AVIUM* COMPLEX STRAINS TO RIFAMPIN AND RIFABUTIN					
		% of Strains Susceptible/Resistant to Different Concentrations of Rifabutin (µg/mL)			
Susceptibility to Rifampin (µg/mL)	Number of Strains	Susceptible to 0.5	Resistant to 0.5 only	Resistant to 1.0	Resistant to 2.0
Susceptible to 1.0	30	100.0	0.0	0.0	0.0
Resistant to 1.0 only	163	88.3	11.7	0.0	0.0
Resistant to 5.0	105	38.0	57.1	2.9	2.0
Resistant to 10.0	225	20.0	50.2	19.6	10.2
TOTAL	523	49.5	36.7	9.0	4.8

Rifabutin *in vitro* MIC_{99} values of ≤0.5 µg/mL, determined by the agar dilution method, for *M. kansasii*, *M. gordonae* and *M. marinum* have been reported; however, the clinical significance of these results is unknown.

INDICATIONS AND USAGE

MYCOBUTIN is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

Clinical Studies

Two randomized, double-blind clinical trials (study 023 and study 027) compared MYCOBUTIN (300 mg/day) to placebo in patients with CDC-defined AIDS and CD4 counts ≤ 200 cells/μL. These studies accrued patients from 2/90 through 2/92. Study 023 enrolled 590 patients, with a median CD4 cell count at study entry of 42 cells/μL (mean 61). Study 027 enrolled 556 patients, with a median CD4 cell count at study entry of 40 cells/μL (mean 58).

Endpoints included the following:

(1) MAC bacteremia, defined as at least one blood culture positive for *M. avium* complex bacteria.

(2) Clinically significant disseminated MAC disease, defined as MAC bacteremia accompanied by signs or symptoms of serious MAC infection, including one or more of the following: fever, night sweats, rigors, weight loss, worsening anemia, and/or elevations in alkaline phosphatase.

(3) Survival

MAC bacteremia

Participants who received MYCOBUTIN were one-third to one-half as likely to develop MAC bacteremia as were participants who received placebo. These results were statistically significant (study 023: $p < 0.001$; study 027: $p = 0.002$).

In study 023, the one-year cumulative incidence of MAC bacteremia, on an intent to treat basis, was 9% for patients randomized to MYCOBUTIN and 22% for patients randomized to placebo. In study 027, these rates were 13% and 28% for MYCOBUTIN-treated and placebo-treated patients, respectively.

Most cases of MAC bacteremia (approximately 90% in these studies) occurred among participants whose CD4 count at study entry was ≤ 100 cells/μL. The median and mean CD4 counts at onset of MAC bacteremia were 13 cells/μL and 24 cells/μL, respectively. These studies did not investigate the optimal time to begin MAC prophylaxis.

Clinically significant disseminated MAC disease

In association with the decreased incidence of bacteremia, patients on MYCOBUTIN showed reductions in the signs and symptoms of disseminated MAC disease, including fever, night sweats, weight loss, fatigue, abdominal pain, anemia, and hepatic dysfunction.

Survival

The one year survival rates in study 023 were 77% for the MYCOBUTIN group and 77% for the placebo group. In study 027, the one year survival rates were 77% for the MYCOBUTIN group and 70% for the placebo group. These differences were not statistically significant.

CONTRAINDICATIONS

Rifabutin is contraindicated in patients who have had clinically significant hypersensitivity to this drug, or to any other rifamycins.

WARNINGS

MYCOBUTIN prophylaxis must not be administered to patients with active tuberculosis. Tuberculosis in HIV-positive patients is common and may present with atypical or extrapulmonary findings. Patients are likely to have a nonreactive purified protein derivative (PPD) despite active disease. In addition to chest X-ray and sputum culture, the following studies may be useful in the diagnosis of tuberculosis in the HIV- positive patient: blood culture, urine culture, or biopsy of a suspicious lymph node.

Patients who develop complaints consistent with active tuberculosis while on MYCOBUTIN prophylaxis should be evaluated immediately, so that those with active disease may be given an effective combination regimen of anti-tuberculosis medications. Administration of single-agent MYCOBUTIN to patients with active tuberculosis is likely to lead to the development of tuberculosis that is resistant both to MYCOBUTIN and to rifampin.

There is no evidence that MYCOBUTIN is effective prophylaxis against *M. tuberculosis*. Patients requiring prophylaxis against both *M. tuberculosis* and *Mycobacterium avium* complex may be given isoniazid and MYCOBUTIN concurrently.

PRECAUTIONS

Because MYCOBUTIN may be associated with neutropenia, and more rarely thrombocytopenia, physicians should consider obtaining hematologic studies periodically in patients receiving MYCOBUTIN prophylaxis.

Information for Patients

Patients should be advised of the signs and symptoms of both MAC and tuberculosis, and should be instructed to consult their physicians if they develop new complaints consistent with either of these diseases. In addition, since MYCOBUTIN may rarely be associated with myositis and uveitis, patients should be advised to notify their physicians if they develop signs or symptoms suggesting either of these disorders.

Urine, feces, saliva, sputum, perspiration, tears, and skin may be colored brown-orange with rifabutin and some of its metabolites. Soft contact lenses may be permanently stained. Patients to be treated with MYCOBUTIN should be made aware of these possibilities.

Drug Interactions

In 10 healthy adult volunteers and 8 HIV-positive patients; steady-state plasma levels of zidovudine (ZDV), an antiretroviral agent which is metabolized mainly through glucuronidation, were decreased after repeated MYCOBUTIN dosing; the mean decrease in C_{max} and AUC was 48% and 32%, respectively. *In vitro* studies have demonstrated that MYCOBUTIN does not affect the inhibition of HIV by ZDV.

Steady-state kinetics in 12 HIV-positive patients show that both the rate and extent of systemic availability of didanosine (ddI), was not altered after repeated dosing of MYCOBUTIN.

MYCOBUTIN has liver enzyme-inducing properties. The related drug rifampin is known to reduce the activity of a number of other drugs, including dapsone, narcotics (including methadone), anticoagulants, corticosteroids, cyclosporine, cardiac glycoside preparations, quinidine, oral contraceptives, oral hypoglycemic agents (sulfonylureas), and analgesics. Rifampin has also been reported to decrease the effects of concurrently administered ketoconazole, barbiturates, diazepam, verapamil, beta-adrenergic blockers, clofibrate, progestins, disopyramide, mexiletine, theophylline, chloramphenicol, and anticonvulsants. Because of the structural similarity of rifabutin and rifampin, MYCOBUTIN may be expected to have some effect on these drugs as well. However, unlike rifampin, MYCOBUTIN appears not to affect the acetylation of isoniazid. When rifabutin was compared with rifampin in a study with 8 healthy normal volunteers, rifabutin appeared to be a less potent enzyme inducer than rifampin. The significance of this finding for clinical drug interactions is not known. Dosage adjustment of drugs listed above may be necessary if they are given concurrently with MYCOBUTIN. Patients using oral contraceptives should consider changing to nonhormonal methods of birth control.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long term carcinogenicity studies were conducted with rifabutin in mice and in rats. Rifabutin was not carcinogenic in mice at doses up to 180 mg/kg/day, or approximately 36 times the recommended human daily dose. Rifabutin was not carcinogenic in the rat at doses up to 60 mg/kg/day, about 12 times the recommended human dose.

Rifabutin was not mutagenic in the bacterial mutation assay (Ames Test) using both rifabutin-susceptible and resistant strains. Rifabutin was not mutagenic in *Schizosaccharomyces pombe* P_1 and was not genotoxic in V-79 Chinese hamster cells, human lymphocytes *in vitro*, or mouse bone marrow cells *in vivo*.

Fertility was impaired in male rats given 160 mg/kg (32 times the recommended human daily dose).

Pregnancy:

Pregnancy Category B: Reproduction studies have been carried out in rats and rabbits given rifabutin using dose levels up to 200 mg/kg (40 times the recommended human daily dose). No teratogenicity was observed in either species. In rats, given 200 mg/kg/day, there was a decrease in fetal viability. In rats, at 40 mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in fetal skeletal variants. In rabbits, at 80 mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxicity and increase in fetal skeletal anomalies. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, rifabutin should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

It is not known whether rifabutin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness of rifabutin for prophylaxis of MAC in children have not been established. Limited safety data are available from treatment use in 22 HIV-positive children with MAC who received MYCOBUTIN in combination with at least two other antimycobacterials for periods from 1 to 183 weeks. Mean doses (mg/kg) for these children were: 18.5 (range 15.0 to 25.0) for infants one year of age; 8.6 (range 4.4 to 18.8) for children 2 to 10 years of age; and 4.0 (range 2.8 to 5.4) for adolescents 14 to 16 years of age. There is no evidence that doses greater than 5 mg/kg daily are useful. Adverse experiences were similar to those observed in the adult population, and included leukopenia, neutropenia and rash. Doses of MYCOBUTIN may be administered mixed with foods such as applesauce.

ADVERSE REACTIONS

MYCOBUTIN was generally well tolerated in the controlled clinical trials. Discontinuation of therapy due to an adverse event was required in 16% of patients receiving MYCOBUTIN compared to 6% of patients receiving placebo in these trials. Primary reasons for discontinuation of MYCOBUTIN were rash (4% of treated patients), gastrointestinal intolerance (3%), and neutropenia (2%).

The following table enumerates adverse experiences that occurred at a frequency of 1% or greater, among the patients treated with MYCOBUTIN in studies 023 and 027.

CLINICAL ADVERSE EXPERIENCES
REPORTED IN ≥ 1% OF PATIENTS TREATED WITH MYCOBUTIN

ADVERSE EVENT	MYCOBUTIN (n = 566) %	PLACEBO (n = 580) %
BODY AS A WHOLE		
Abdominal Pain	4	3
Asthenia	1	1
Chest Pain	1	1
Fever	2	1
Headache	3	5
Pain	1	2
DIGESTIVE SYSTEM		
Anorexia	2	2
Diarrhea	3	3
Dyspepsia	3	1
Eructation	3	1
Flatulence	2	1
Nausea	6	5
Nausea and Vomiting	3	2
Vomiting	1	1
MUSCULOSKELETAL SYSTEM		
Myalgia	2	1
NERVOUS SYSTEM		
Insomnia	1	1
SKIN AND APPENDAGES		
Rash	11	8
SPECIAL SENSES		
Taste Perversion	3	1
UROGENITAL SYSTEM		
Discolored Urine	30	6

CLINICAL ADVERSE EVENTS REPORTED IN < 1% OF PATIENTS WHO RECEIVED MYCOBUTIN

Considering data from the 023 and 027 pivotal trials, and from other clinical studies, MYCOBUTIN appears to be a likely cause of the following adverse events which occurred in less than 1% of treated patients: flu-like syndrome, hepatitis, hemolysis, arthralgia, myositis, chest pressure or pain with dyspnea, and skin discoloration.

The following adverse events have occurred in more than one patient receiving MYCOBUTIN, but an etiologic role has not been established: seizure, paresthesia, aphasia, confusion, and non-specific T wave changes on electrocardiogram.

When MYCOBUTIN was administered at doses from 1050 mg/day to 2400 mg/day, generalized arthralgia and uveitis were reported. These adverse experiences abated when MYCOBUTIN was discontinued.

The following table enumerates the changes in laboratory values that were considered as laboratory abnormalities in studies 023 and 027.

PERCENTAGE OF PATIENTS WITH LABORATORY ABNORMALITIES

LABORATORY ABNORMALITIES	MYCOBUTIN (n = 566) %	PLACEBO (n = 580) %
Chemistry:		
Increased Alkaline Phosphatase[1]	<1	3
Increased SGOT[2]	7	12
Increased SGPT[2]	9	11
Hematology:		
Anemia[3]	6	7
Eosinophilia	1	1
Leukopenia[4]	17	16
Neutropenia[5]	25	20
Thrombocytopenia[6]	5	4

INCLUDES GRADE 3 OR 4 TOXICITIES AS SPECIFIED:
1 all values > 450 U/L
2 all values > 150 U/L
3 all hemoglobin values < 8.0 g/dL
4 all WBC values < 1,500/mm³
5 all ANC values < 750/mm³
6 all platelet count values < 50,000/mm³

The incidence of neutropenia in patients treated with MYCOBUTIN was significantly greater than in patients treated with placebo ($p = 0.03$). Although thrombocytopenia was not significantly more common among MYCOBUTIN treated patients in these trials, MYCOBUTIN has been clearly linked to thrombocytopenia in rare cases. One patient in study 023 developed thrombotic thrombocytopenic purpura, which was attributed to MYCOBUTIN.

ANIMAL TOXICOLOGY

Liver abnormalities, (increased bilirubin and liver weight), occurred in all species tested, in rats at doses 5 times, in monkeys at doses 8 times, and in mice at doses 6 times the recommended human daily dose. Testicular atrophy occurred in baboons at doses 4 times the recommended human dose, and in rats at doses 40 times the recommended human daily dose.

OVERDOSAGE

No information is available on accidental overdosage in humans.

Treatment

While there is no experience in the treatment of overdose with MYCOBUTIN, clinical experience with rifamycins suggest that gastric lavage to evacuate gastric contents (within a few hours of overdose), followed by instillation of an activated charcoal slurry into the stomach, may help absorb any remaining drug from the gastrointestinal tract.

Rifabutin is 85% protein bound and distributed extensively into tissues (Vss:8 to 9 L/kg). It is not primarily excreted via the urinary route (less than 10% as unchanged drug), therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifabutin from the body in a patient with MYCOBUTIN overdose.

DOSAGE AND ADMINISTRATION

It is recommended that 300 mg of MYCOBUTIN be administered once daily. For those patients with propensity to nausea, vomiting, or other gastrointestinal upset, administration of MYCOBUTIN at doses of 150 mg twice daily taken with food may be useful.

HOW SUPPLIED

MYCOBUTIN™ (rifabutin capsules) is supplied as hard gelatin capsules having an opaque red-brown cap and body, imprinted with ADRIA/MYCOBUTIN in white ink, each containing 150 mg of rifabutin.
MYCOBUTIN is available as follows:

NDC 0013-5301-17 Bottles of 100 capsules

Keep tightly closed and dispense in a tight container as defined in the USP. Store at controlled room temperature, 15° to 30°C (59° to 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
FARMITALIA CARLO ERBA
ASCOLI PICENO, ITALY

For:
ADRIA LABORATORIES
COLUMBUS, OHIO 43216

4

United States Patent [19]

Marsili et al.

[11] **4,219,478**

[45] * **Aug. 26, 1980**

[54] **RIFAMYCIN COMPOUNDS**

[75] Inventors: **Leonardo Marsili; Vittorio Rossetti; Carmine Pasqualucci**, all of Milan, Italy

[73] Assignee: **ARCHIFAR Laboratori Chimico Farmacologici S.p.A.**, Rovereto, Italy

[*] Notice: The portion of the term of this patent subsequent to Apr. 25, 1995, has been disclaimed.

[21] Appl. No.: **913,107**

[22] Filed: **Jun. 6, 1978**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 694,589, Jun. 10, 1976, Pat. No. 4,086,225.

[30] **Foreign Application Priority Data**

Jun. 13, 1975 [IT] Italy 5174 A/75

[51] **Int. Cl.²** **C07D 491/20**

[52] **U.S. Cl.** ..... **260/239.3 P; 424/264**

[58] **Field of Search** ..... 260/239.3 P

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,086,225 4/1978 Marsili et al. ..... 260/239.3 P

FOREIGN PATENT DOCUMENTS

2626296 12/1976 Fed. Rep. of Germany .... 260/239.3 P

Primary Examiner—Alan L. Rotman
Assistant Examiner—Robert T. Bond
Attorney, Agent, or Firm—Oblon, Fisher, Spivak, McClelland & Maier

[57] **ABSTRACT**

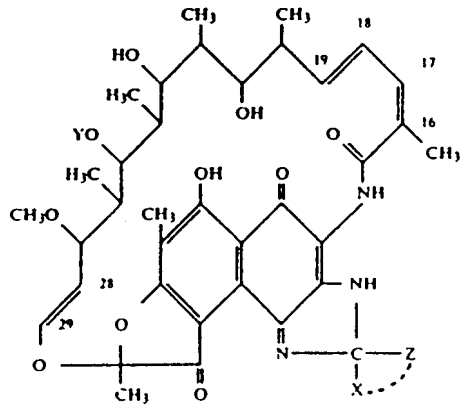
Oxidized rifamycin compounds having high antibiotic activity as obtained by reacting 3-amino-4-deoxo-4-imino-rifamycin S or related compounds with a ketone.

5 Claims, No Drawings

RIFAMYCIN COMPOUNDS

This application is concerned with an invention related to that disclosed and claimed in our prior application Ser. No. 694,589, filed June 10, 1976, now U.S. Pat. No. 4,086,225, issued Apr. 25, 1978.

The invention of U.S. Pat. No. 4,086,225 and this invention relates to novel rifamycin compounds having high antibiotic activity. Such compounds are selected from the group consisting of the compounds having the following formula:



(I)

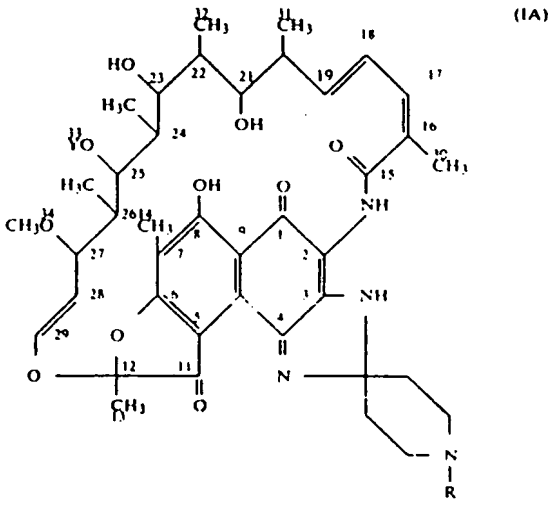
wherein; X is an alkyl having less than 5 carbon atoms; Y is —H or —$COCH_3$; Z is selected from the group consisting of alkyl with less than 5 carbon atoms, alkoxy-alkyl with less than 6 carbon atoms, hydroxyalkyl with less than 4 carbon atoms, carboxyalkyl with less than 5 carbon atoms, carbalkoxyalkyl with less than 6 carbon atoms, halogen-alkyl with less than 4 carbon atoms, N,N-dialkylaminoalkyl, in particular dialkylaminoalkyl having less than 6 carbon atoms, arylalkyl with less than 10 carbon atoms, cycloalkyl, in particular cycloalkyl having less than 7 carbon atoms, and X and Z along with the C atom to which they are bonded form a ring selected from the group consisting of a hydrocarbon ring with less than 7 carbon atoms, a hydrocarbon ring with less than 7 carbon atoms substituted with at least one radical selected from the group consisting of alkyl with less than 4 carbon atoms, halogen and carbalkoxy, in particular carbalkoxy with less than 4 carbon atoms, a heterocyclic ring with less than 7 atoms containing one N atom, in particular the piperidine ring, a heterocyclic ring with less than 7 atoms, containing one N atom, in particular the piperidine ring, and substituted with a radical selected from the group comprising linear alkyl having from 1 to 8 carbon atoms, branched alkyl having from 3 to 8 carbon atoms, alkenyl having 3 or 4 carbon atoms, cycloalkyl having from 3 to 6 carbon atoms, alkoxyalkyl having from 3 to 7 carbon atoms, arylalkyl with less than 9 carbon atoms, alkyl-furyl having 5 or 6 carbon atoms, alkyl tetrahydrofuryl having 5 or 6 carbon atoms, carbalkoxy, in particular carbalkoxy with less than 4 carbon atoms and alkanoyl having from 2 to 6 carbon atoms, haloalkanoyl having from 2 to 6 carbon atoms and one haloatom only, and 16, 17, 18, 19-tetrahydroderivatives and 16, 17, 18, 19, 28, 29-hexahydroderivates thereof.

The term "aryl" is used herein, to designate aryl hydrocarbon.

In the parent application, Ser. No. 694,589, it is stated that an alkyl substituent on the N-containing heterocyclic ring may have less than 4 carbon atoms and an acyl substituent less than 5 carbon atoms and such substituents are included in the invention common to that of the present invention and that of our Pat. No. 4,086,225, referred to above.

A substituent on the N-containing heterocyclic ring is preferably positioned on a nitrogen atom of that ring.

Rifamycin compounds having antibiotic activity of formula

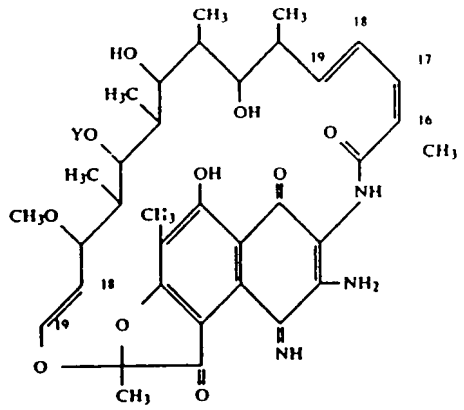


(IA)

wherein R is a radical selected from the group consisting of linear alkyl having 4 to 8 carbon atoms, branched alkyl having 4 to 8 carbon atoms, alkenyl having 3 or 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, alkoxyalkyl having 3 to 7 carbon atoms, alkyl-furyl having 5 or 6 carbon atoms, alkyl tetrahydrofuryl having 5 or 6 carbon atoms, alkanoyl having 5 or 6 carbon atoms, and monohaloalkanoyl having 2 to 6 carbon atoms, and Y is —H or —$COCH_3$, and their preparation, are the subject of the present invention. Also included in the present invention are 16, 17, 18, 19-tetrahydroderivatives and the 16, 17, 18, 19, 28, 29-hexahydro-derivatives thereof.

Rifamycin compounds according to the present invention have high antibacterial activity, particularly on Mycobacterium Tuberculosis. Such compounds are in the form of powders from pink to violet color, are soluble in most organic solvents and most are water insoluble.

Such rifamycin compounds are obtained by a method wherein a rifamycin compound having the formula



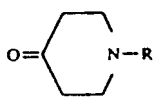
(II)

wherein Y is —H or —$COCH_3$; its 16, 17, 18, 19-tetrahydroderivatives and 16, 17, 18, 19, 28, 29-hexahydroderivatives, is reacted with a ketone having the formula

(III)

wherein X and Z are those as above defined, and X and Z along with CO form a ring selected from the group consisting of a hydrocarbon ring with less than 7 carbon atoms, a hydrocarbon ring with less than 7 carbon atoms substituted with at least one radical selected from the group comprising alkyl with less than 4 carbon atoms, halogen and carbalkoxy, as one having less than 4 carbon atoms, a heterocyclic ring with less than 7 atoms containing one N atom, such as the piperidine ring, a heterocyclic ring with less than 7 atoms containing one N atom, such as the piperidine ring, and substituted with a radical selected from the group consisting of linear alkyl having from 1 to 8 carbon atoms, branched alkyl having from 3 to 8 carbon atoms, alkenyl having 3 or 4 carbon atoms, cycloalkyl having from 3 to 6 carbon atoms, alkoxyalkyl having from 3 to 7 carbon atoms, arylalkyl with less than 9 carbon atoms, alkyl-furyl having 5 or 6 carbon atoms, alkyl tetrahydrofuryl having 5 or 6 carbon atoms, carbalkoxy, in particular carbalkoxy having less than 4 carbon atoms, alkanoyl having from 2 to 6 carbon atoms, and haloalkanoyl having from 2 to 6 carbon atoms and one haloatom only.

When formula III corresponds to the piperidine ring or the substituted piperidine ring, a suitable ketone is of the formula



(IIIA)

where R is hydrogen or a substituent on the piperidine ring as defined following formula (I) and formula (IA).

The compound of formula (II) and methods of preparing the same are disclosed in applicants' patent application Ser. No. 680,771, filed Apr. 27, 1976, now U.S. Pat. No. 4,017,481, issued Apr. 12, 1977.

It has been found that the reaction of a ketone of formula (III) with the compound of formula (II) is more readily carried out and with improved yields when such a reaction is effected in the presence of acetic acid and a reducing agent selected from the group consisting of zinc and iron. Ammonium acetate together with zinc is also helpful in achieving improved results.

In order that the present invention be more clearly understood, some unrestrictive examples thereof will now be shown.

EXAMPLE 1

10 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 20 ml cyclohexanone. The solution was added with 1 g zinc, 20 ml acetic acid and stirred for 60 minutes at room temperature. Unreacted zinc was filtered, and the reaction solution was added with 100 ml dichloromethane, washed with water, dried on sodium sulphate and evaporated to dryness. The residue was dissolved again with 30 ml dichloromethane, the solution added with 200 ml petroleum ether, the precipitate obtained was filtered, then concentrating to 50 ml. 4.8 g were crystallized of a product of formula (I), wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a cyclohexylidene radical. The chemical-physical characteristics of the product are as follows:

the electronic absorption spectrum in methanol shows peaks at 495, 315 and 275 nm;

I.R. spectrum in nujol shows absorption bands in the region about 3250, and then at 1725, 1665, 1600, 1560, 1515, 1295, 1250, 1775-1155, 1060, 970, 920, 890, 765 and 725 cm^{-1};

nuclear magnetic resonance spectrum in deuterated-chloroform, using tetrametylsilane as internal standard, shows the most significant peaks at θ: 0.60(d); 0.83(d); 1.05(d); 3.10(s); 4.81(dd); 5.15(dd); 8.23(s); 9.20(s) and 14.75(s) p.p;m. Also the disappearance of the last three said peaks, when in presence of deuterated water is characteristic.

EXAMPLE 2

10 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 25 ml methylisobutylketone. The solution was added with 1 g zinc, 50 ml acetic acid and heated at 40° C. for 30 minutes. Excess zinc was filtered, the reaction solution was added with 100 ml dichloromethane and washed with water. After drying on sodium sulphate and concentration to 20 ml, 100 ml cyclohexane and 50 petroleum ether were added. The solution was filtered and the filtered solution was evaporated to dryness.

Yield: 4.4 g product of formula (I), wherein Y is —$COCH_3$, X is methyl and Z is isobutyl, with the following chemical-physical characteristics:

the electronic absorption spectrum in methanol shows peaks at 500, 310 and 275 nm;

I.R. spectrum in nujol oil shows the most significant peaks at: 3400 (sh), 3250, 1725, 1620, 1500, 1560, 1510, 1415, 1290, 1250, 1155, 1060, 970, 945, 915, 890, 810 and 720 cm^{-1}.

EXAMPLE 3

8 g 3-amino-4-deoxo-4-imino-rifamycin S were mixed with 2.5 g iron and dissolved in 15 ml acetone and 15 ml acetic acid. After stirring at 35° C. for 15 minutes, excess iron was filtered and the solution poured into 600 ml water. The solution was filtered, washed with water, the aqueous phase extracted with toluene after correcting pH to 7 with bisodic phospahte. Toluene was concentrated to 20 ml and then diluted with 80 ml cyclo-

hexane. After filtering, the mixture of the two solvents was evaporated, obtaining 3.5 g product of formula (I), wherein Y is —$COCH_3$, Z and X are methyl, and with the following chemical-physical characteristics:

the electronic absorption spectrum in methanol shows peaks at 490, 350(sh), 315 and 270 nm;

I.R. spectrum in nujol shows the most significant peaks at: 3400 (sh), 3250, 1730, 1675, 1650(sh), 1605, 1565, 1515, 1420, 1300, 1250, 1170, 1085, 1065, 975, 950, 930, 895, 815 and 690 cm^{-1}.

EXAMPLE 4

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 25 ml dioxane, added with 6 g 1-methyl-4-piperidone dissolved in 5 ml dioxane and heated at 70° C. for 10 minutes. The solution was poured into 400 ml water containing 20 g sodium chloride, the precipitate filtered, the filtrate extracted with chloroform, the organic phase dried on sodium sulphate and the solvent evaporated. The residue obtained was dissolved in benzene and the solution extracted with an aqueous solution of bisodic phosphate. Benzene was washed with water, the solution dried on sodium sulphate and then evaporated to dryness. Yield: 2.2 g product of formula (I), wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4-(1-methyl) piperidinylidene radical. The chemical-physical characteristics of the product are as follows:

The electronic absorption spectrum in methanol shows peaks at 485, 350(sh), 310 and 270 nm;

I.R. spectrum in nujol shows the most significant peaks at: 3400(sh), 3250, 1730, 1670, 1650(sh), 1605, 1565, 1515, 1420, 1300, 1255, 1180, 1160, 1065, 1015, 975, 950(sh), 920, 895, 815, 770 and 695 cm^{-1};

nuclear magnetic resonance spectrum in deuterated chloroform, using tetramethylsilane as internal standard, shows the most significant peaks at θ: −0.16(d); 0.60(d); 0.86(d); 1.04(d); 1.77(s); 2.02(s); 2.06(s); 2.32(s); 2.49(s); 3.10(s); 4.82(d); 5.14(dd); 5.70–6.60(m); 7.0–7.4(m); 8.27(s); 8.97(s) and 14.67(s) p.p.m. Also the disappearance of the last three said peaks, when in the presence of deuterated water, is characteristic.

EXAMPLE 5

8 g 3-amino-4-deoxo-4-imino-rifamycin S were reacted with 1 g zinc, 15 ml tetrahydrofuran, 8.5 ml 1-carbethoxy-4-piperidone and 25 ml acetic acid at 50° C. for 10 minutes. The reaction mixture was filtered and diluted with 200 ml xylene, washed with a phosphate buffer solution at pH 7.5, then with water and finally dried on sodium sulphate. Xylene was then evaporated to obtain 100 ml solution, which was diluted with 150 ml petroleum ether, filtered and evaporated to dryness. The residue obtained was added again with petroleum ether, filtered and dried. Yield: 5 g product of formula (I), wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a 4-(1-carbethoxy)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 500, 360(sh), 312 and 275 nm.

EXAMPLE 6

8 g 3-amino-4-deoxo-4-imino-rifamycin S were reacted with 1 g zinc, 10 ml tetrahydrofuran, 12 ml chloroacetone and 25 ml acetic acid. After 5 minutes at 60° C., the reaction was completed and after filtering unreacted zinc, the solution was poured into 800 ml buffered solution at pH 7.5 and containing 5 g ascorbic acid. The precipitate obtained was filtered, washed with water and vacuum dried at 40° C. Finally, the residue was continuously extracted with petroleum ether and by solvent evaporation 3.6 g product of formula (I) are obtained, wherein Y is —$COCH_3$, X is methyl and Z is chloromethyl.

The electronic absorption spectrum in methanol shows peaks at 495, 270, 238 and 210 nm.

EXAMPLE 7

8 g 3-amino-4-deoxo-4-imino-rifamycin S were reacted with 1 g zinc, 15 ml tetrahydrofuran, 8 ml 1-benzyl-4-piperidone and 30 ml acetic acid. After stirring at 60° C. for 15 minutes, unreacted zinc was filtered, then adding 1 g ascorbic acid, diluting with 300 ml xylene and washing with phosphate buffer solution at pH 7.5 and then with water. After drying the solution on sodium sulphate, the solvent was evaporated to dried residue, which was then continuously extracted with petroleum ether.

After solvent evaporation, 2.5 g product of formula (I) were then obtained, wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4-(1-benzyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 500, 315 and 275 nm.

EXAMPLE 8

8 g 3-amino-4-deoxo-4-imino-16, 17, 18, 19-tetrahydrorifamycin S were reacted with 1 g zinc, 15 ml tetrahydrofuran, 6 ml diethylaminoacetone and 30 ml acetic acid. After stirring at room temperature for 15 minutes, excess zinc was filtered, adding 1 g ascorbic acid and dropwise pouring the solution into 700 ml water.

The precipitate obtained was filtered and dissolved again in minimum volume of methyl alcohol. The methanol solution was diluted with 250 ml ethyl ether and then extracted with phosphate buffer solution at pH 7.5. The aqueous layer was acidified to pH 3 and then extracted with chloroform. The chloroform layer was washed with water, dried on sodium sulphate and evaporated to dryness. Thus, 0.8 g were obtained of 16, 17, 18, 19-tetrahydroderivative of a product of formula (I), wherein Y is —$COCH_3$, X is methyl and Z is diethylaminomethyl.

The electronic absorption spectrum in methanol shows peaks at 455 and 320 nm.

EXAMPLE 9

8 g 3-amino-4-deoxo-4-imino-16, 17, 18, 19, 28, 29-hexahydro-25-desacetyl-rifamycin S were reacted with 1 g zinc, 15 ml tetrahydrofuran, 4.5 g 1-acetyl-4-piperidone and 25 ml acetic acid. After stirring at room temperature for 30 minutes, unreacted zinc was filtered, adding 1 g ascorbic acid and diluting with 300 ml ethyl ether. The ether solution was thoroughly washed with water and then dried on sodium sulphate. Then, the residue was diluted with 50 ml petroleum ether, filtered and evaporated to dryness. 1.7 g 16, 17, 18, 19, 28, 29-hexahydroderivative of a product of formula (I) were obtained, wherein Y is —H and X and Z, along with the C atom to which they are bonded, form a 4-(1-acetyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 495, 315 and 275 nm.

EXAMPLE 10

8 g 3-amino-4-deoxo-4-imino-rifamycin S were reacted with 1 g zinc, 15 ml tetrahydrofuran, 2.5 g methylcyclopropylketone and 25 ml acetic acid. After 30 minutes at 50° C., unreacted zinc was filtered, the solution was diluted with 100 ml benzene and 300 ml ethyl ether and then washed with phosphate buffer solution at pH 7.5 and finally with water. The organic layer was evaporated, the residue reacted again with 30 ml methyl alcohol and after addition of 5 ml water containing 1 g sodium ascorbate, the solution was dropwise poured into 300 ml saturated aqueous solution of sodium metabisulphite. The precipitate obtained was filtered, washed with water and dried, 2.2 g product of formula (I) were obtained, wherein Y is —$COCH_3$, X is methyl and Z is cyclopropyl.

The electronic absorption spectrum in methanol shows peaks at 500 and 320 nm.

EXAMPLE 11

8 g 3-amino-4-deoxo-4-imino-rifamycin S dissolved in 25 ml tetrahydrofuran were dropwise added to a mixture comprising 1 g zinc, and 5 g 4-phenyl-butan-2-one preheated at 60° C. After stirring at 60° C. for 30 minutes, unreacted zinc was filtered, the mixture was added with 1 g ascorbic acid and diluted with 250 ml benzene. The mixture was then thoroughly washed with water, dried on sodium sulphate and benzene evaporated.

The residue obtained was dissolved in minum volume of methyl alcohol, the solution was treated with 5 ml water containing 1 g sodium ascorbate and then poured into 1000 ml water. The precipitate obtained was filtered, washed with water and dried. The product was dissolved again in 40 ml benzene, added with 80 ml petroleum ether, filtered and the solution was evaporated. The residue obtained of violet colour was added with water and filtrate. After drying, 2.8 g product of formula (I) were obtained, wherein Y is —$COCH_3$, X is methyl and Z is β-phenethyl. The electronic absorption spectrum in methanol shows peaks at 500 and 315 nm.

EXAMPLE 12

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml dichloromethane and reacted with 2.6 g 1-n-hexyl-4-piperidone at +5° C. for 48 hours. The solution was diluted with 600 ml ethyl ether, filtered and washed with water.

The organic phase was dried on sodium sulphate and then evaporated to dryness. The residue was extracted with ligroin and the violet solution evaporated to dryness.

Yield: 2.5 g product of formula (I), wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4-(1-n-hexyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 497, 314, 278 and 239 nm.

EXAMPLE 13

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml tetrahydrofuran. 4 g 1-(1',3'-dimethyl) butyl-4-piperidone, 0.5 g zinc and 0.5 g ammonium acetate were added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was worked up as in the example No. 12 obtaining 3.5 g of a product of formula (I), wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a 4-[1-(1',3'-dimethyl)-butyl]-piperidinylidene radical. The electronic absorption spectrum in methanol shows peaks at 500, 315, 277 and 240 nm.

EXAMPLE 14

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml tetrahydrofuran. 1.8 gl-methallyl-4-piperidone, 0.2 g zinc and 0.2 g ammonium acetate were added and the mixture was allowed to stand at +5° C. for one night.

Reaction mixture was worked up as in the example No. 12 obtaining 5.5 g product of formula (I), wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4-(1-methallyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peacks at 498, 313, 275 and 238 nm.

EXAMPLE 15

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml tetrahydroduran. 3 g 1-cyclohexyl-4-piperidone, 0.2 g zinc and 0.2 ammonium acetate were added and the mixture was sittred 2.5 hours at room temperature. Unreacted zinc was filtered and the solution diluted with 1000 ml ethyl ether.

The ethereal solution was washed with buffer sodium phosphate solution at pH 7.8 and then extracted with diluted acetic acid. The violet aqueous solution was extracted with chloroform. the organic phase was washed and then dried on sodium sulfate. The chloroform was evaporated to dryness. Yield: 3.8 g product of formula (I), wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4-(1-cyclohexyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 498, 312, 273 and 235 nm.

EXAMPLE 16

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml tetrahydroduran. 0.5 g zinc, 0.5 g ammonium acetate and 5.5 g 1-(methylfuryl)-4-piperidone were added and the mixture was stirred at room temperature for 24 hours.

The reaction mixture was filtered, diluted with 500 ml diethyl ether and washed with water.

The organic phase was concentrated at 250 ml and then extracted with aqueous diluted acetic acid.

The violet, aqueous solution was extracted with dichloromethane and the organic phase, washed with water and dried on sodium sulfate was evaporated to dryness.

Yield: 3.3 g product of formula (I) wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a 4-(1-methylfuryl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 497, 316, 276 and 240 nm.

EXAMPLE 17

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml tetrahydrofuran and dropped at 50° C. in a mixture of 15 ml tetrahydrofuran, 5 ml acetic acid, 1 g zinc and 5 g 1-(methyl-tetrahydrofuryl)-4-piperidone.

Heating is continued for 30 minutes and then the reaction mixture was worked up as in the example No. 16.

Yield: 2.1 g product of formula (I) wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a 4 (1-methyltetrahydrofuryl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 495, 314, 275 and 239 nm.

EXAMPLE 18

32 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 200 ml tetrahydrofuran. 9 g 4-piperidone monohydrate hydrochloride, 10 g ammonium acetate and 0.4 g zinc were added and the mixture was stirred at room temperature for 12 hours.

The reaction mixture was filtered and dropped into 1500 ml diluted acetic acid. After filtration the aqueous solution was neutralized with sodium bicarbonate at pH 6 and then extracted twice with dichloromethane.

Yield: 13.4 g product of formula (I), wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a 4-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 500, 315, 275 and 240 nm.

EXAMPLE 19

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 50 ml tetrahydrofuran. 0.3 g zinc, 0.3 g ammonium acetate and 2.5 g 1-chloroacetyl-4-piperidone were added and the mixture allowed to react at +5° C. for 48 hours.

The reaction mixture was filtered and diluted with 150 ml dichloromethane and 800 ml cyclohexane.

The solution was filtered again, washed with buffer sodium phosphate solution at pH 7.5 and then with water.

The solvent was evaported under vacuum and the residue was crystallized from cyclohexane.

Yield: 3.2 g product of formula (I), wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4-(1-chloroacetyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 497, 310, 273 and 235 nm.

EXAMPLE 20

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml tetrahydrofuran. 0.5 g zinc, 5 ml acetic acid and 4.5 g 1-n-octyl-4-piperidone were added and the mixture was stirred ten minutes at room temperature.

Unreacted zinc was filtered and the solution diluted with 700 ml diisopropyl-ether. The solution was filtered again and concentrated to 300 ml under vacuum.

300 ml petroleum ether were added and the solution was filtered once more. After evaporation of the solvent the oily residue was dissolved in 40 ml methanol and the solution was dropped in 400 ml water.

The obtained precipitate was filtered, washed with water and dried at 40° C. under vacuum.

Yield: 3.8 g product of formula (I), wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4-(1-n-octyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 497, 310, 274 and 236 nm.

EXAMPLE 21

16 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 100 ml tetrahydrofuran. 1 g zinc, 0.5 g ammonium acetate and 8 g 1-(3'-methoxy) propyl-4-piperidone were added and the mixture was stirred at room temperature for 60'.

The reaction mixture was filtered, diluted with 1500 ml xylene and washed with water. The organic phase was extracted with diluted acetic acid and then discharged.

The aqueous solution, buffered at pH 7 with sodium phosphate solution, was extracted with dichloromethane.

After dilution with petroleum ether the violet solution was filtered and then evaporated to dryness. Yield: 3.0 g product of formula (I), wherein Y is —$COCH_3$, and X and Z, along with the C atom to which they are bonded, form a 4[1-(3'-methoxy-propyl)] piperidinylidene radical.

Thin layer chromatography on silica gel plates, using chloroform-methanol 9:1 as mobile phase, showed one violet spot with Rf=0.48.

EXAMPLE 22

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 40 ml tetrahydrofuran. 0.5 g zinc, 0.5 g ammonium acetate and 4.5 g 1-(1',4'-dimethyl) pentyl-4-piperidone were added and the mixture was stirred at room temperature for 30'.

The reaction mixture was worked up as in the example No. 21.

Yield: 5.0 g product of formula (I) wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a 4-[1-(1',4'-dimethyl-pentyl)-]piperidinylidene radical.

Thin layer chromatography on silica gel plates, using chloroform-methanol 9:1 as mobile phase, showed one violet spot with Rf=0.52.

EXAMPLE 23

8 g 3-amino-4-deoxo-4-imino-rifamycin S were dissolved in 50 ml tetrahydrofuran. 0.2 g zinc, 0.2 g ammonium acetate and 3 g 1-pivaloyl-4-piperidone were added and the mixture was kept at 0° C. for 3 days. The reaction mixture was filtered, diluted with 300 ml diethyl ether and washed with buffer sodium phosphate solution at pH 7.5. The organic phase was washed with water, dried on sodium sulfate and evaporated to dryness.

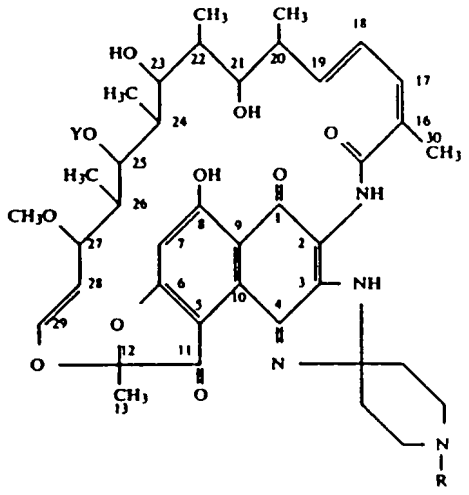
The residue was crystallized from cyclohexane.

Yield: 7 g product of formula I wherein Y is —$COCH_3$ and X and Z, along with the C atom to which they are bonded, form a 4-(1-pivaloyl)-piperidinylidene radical.

The electronic absorption spectrum in methanol shows peaks at 497, 316, 276 and 238 nm.

What we claim is:

1. A rifamycin compound having the formula



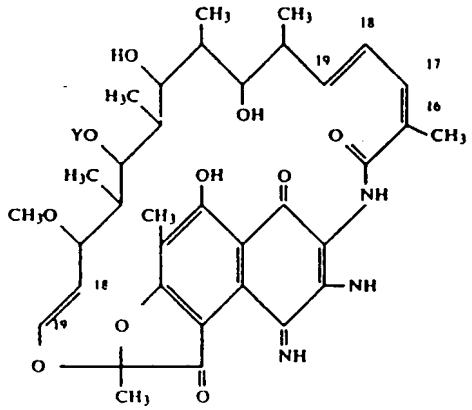
wherein R is a radical selected from the group consisting of linear alkyl having 4 to 8 carbon atoms, branched alkyl having 4 to 8 carbon atoms, and Y is —H or —$COCH_3$, and the 16, 17, 18, 19-tetrahydro derivatives and the 16, 17, 18, 19, 28, 29-hexahydro derivatives thereof.

2. The compound of claim 1, wherein the radical R is selected from the group consisting of linear and branched alkyls having 4 or 5 carbon atoms.

3. The compound of claim 1 wherein the radical R is linear alkyl having 4 to 8 carbon atoms.

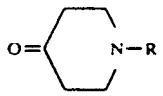
4. The compound of claim 1 wherein the radical R is branched alkyl having 4 to 8 carbon atoms.

5. A method of preparing a rifamycin compound of claim 3, which comprises reacting a compound having the formula



(II)

wherein Y is —H or —$COCH_3$, its 16, 17, 18, 19-tetrahydroderivatives or its 16, 17, 18, 19, 28, 29-hexahydroderivatives, with a ketone having the formula



where R is defined in claim 3.

* * * * *

)03-0
)f
)01-0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Leonardo Marsili et al	
Serial Number: 913,107	Group Art Unit: 121
Filed: June 6, 1978	Examiner: BOND
For: RIFAMYCIN COMPOUNDS	

TERMINAL DISCLAIMER

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Your petitioners LEONARDO MARSILI of Milano 2 - Segrate - Milan, Italy, VITTORIO ROSSETTI of Viale Gavazzi, 52 - Melzo, Milan, Italy, CARMINE PASQUALUCCI of Via Crimea, 23 - Milan, Italy, represent that we are the inventors of the above-identified application and we hereby disclaim the terminal part of any patent granted on the above-identified application, which would extend beyond the expiration date of United States Patent Number 4,086,225, and hereby agree that any patent so granted on the above-identified application shall be enforceable only for and during such period that the legal title of said patent shall be the same as the legal title of the United States Patent Number 4,086,225, this agreement to run with any patent granted on the above-identified application and to be binding upon the grantee, its successors or assigns.

We declare further that all statements made herein of our own

knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: December 13, 1978 — Leonardo Marsili
(Leonardo Marsili)

Date: December 15, 1978 — Vittorio Rossetti
(Vittorio Rossetti)

Date: December 14, 1978 — Carmine Pasqualucci
(Carmine Pasqualucci)

The undersigned, representative of Archifar Laboratori Chimico Farmacologici S.p.A., of Corso Verona 165, Rovereto, Italy, being assignee of total interest of this application, assignment of which is enclosed herewith, concur and agree with this statement.

Date: _____ By: _____
Legal Representative of Archifar Laboratori Chimico Farmacologici S.p.A.

Title: _____

6

5)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

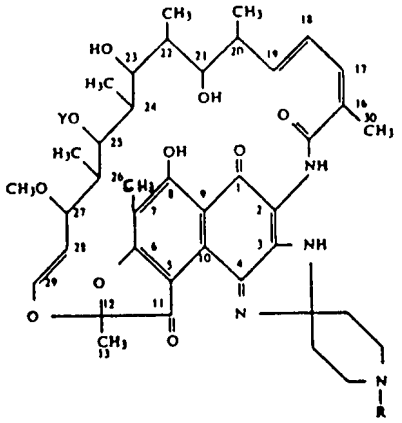
PATENT NO. : 4,219,478

DATED : June 26, 1980

INVENTOR(S) : LEONARDO MARSILI ET AL

It is certified that error appears in the above—identified patent and that said Letters Patent is hereby corrected as shown below:

The structural formula at column 11, lines 1-22 should read as follows --



--

The structural formula at column 12, lines 6-22 should read as follows

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

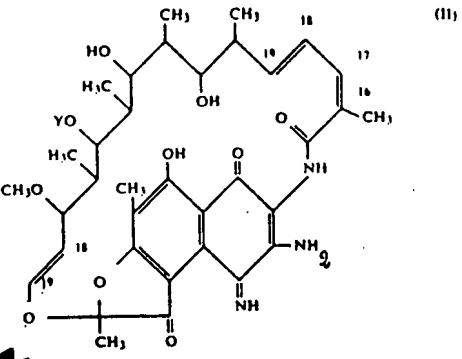
PATENT NO. : 4,219,478

DATED : June 26, 1980

INVENTOR(S) : RIFAMYCIN COMPOUNDS

It is certified that error appears in the above—identified patent and that said Letters Patent is hereby corrected as shown below:

--



(II)

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Signed and Sealed this

Fourteenth Day of April 1981

Attest:

Ruth M. Wray

Attesting Officer

RENE D. TEGTMEYER

Acting Commissioner of Patents and Trademarks

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

REC'D

FEB 2 7 1986

DRA

FEB 24 1986

IND 27,934

ADRIA LABORATORIES, DIV. OF ERBAMONT INC.
P.O. BOX 16529
COLUMBUS, OH 43216-6529

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	27, 934
Sponsor:	ADRIA LABORATORIES
Name of Drug:	RIFABUTIN
Date of Submission:	FEBRUARY 17, 1986
Date of Receipt:	FEBRUARY 21, 1986

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

File → IND
cc FD4/C

U.S. GOVERNMENT PRINTING OFFICE-1984-447-553/7406

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

Should you have any questions concerning this IND, please call:

Consumer Safety Officer MR. JAMES D. BONA
(301) 443- 6797

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drugs and Biologics, HFN-815
Attention: DOCUMENT CONTROL ROOM (12B-30)
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

James D. Bona

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drugs and Biologics

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228e (5/84)

U.S. GOVERNMENT PRINTING OFFICE: 1984 - 444-900/7357

ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Edwards Inc
5000 Post Road Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

April 7, 1986

AIRBOURNE EXPRESS

Edward Tabor, M.D.
Director
Division of Anti-Infective Drug
Products (HFN-815)
ATTN: Document Control Room (12B-30)
Office of Biologics Research & Review
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IND 27,934
Rifabutin

Dear Dr. Tabor:

On February 17, 1986 we submitted a pre-IND submission to Jack Davitt, pursuant to his request, summarizing the pharmacology, toxicology and antimicrobial activity of rifabutin.

We are now submitting the remainder of information to complete the IND. This includes the manufacturing and controls data for the product, and clinical background information, brochure, development plan and protocol for Dr. Siegal's phase I-II to determine the activity and safety of rifabutin in patients with AIDS related complex.

In view of the fact that clinical trials with rifabutin AIDS patients are currently ongoing under the Communicable Disease Centers' IND and Dr. Siegal's investigator-sponsored IND, we are requesting waiver of the 30-day delay.

If you have any questions concerning this IND, please contact me at the following number: 614/764-8129.

Sincerely yours,

Lowell L. Irminger
Director Drug Regulatory Affairs

LLI/bd
enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

REC'D

JUN 5 1986

DRA

JUN 0 2 1986

IND 27,934

Lowell L. Irminger, M.D.
Adria Laboratories
P.O. Box 16529
Columbus, OH 43216-6529

Dear Dr. Irminger:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND) for Ansamycin and the telephone conversation on April 18, 1986 between Dr. Ellen Cooper and Dr. Frederick Siegel and the conversation on April 18, 1986 between Dr. Ellen Cooper and yourself.

Our review of the protocol indicates that it is reasonably safe to proceed with the study, as indicated to you on April 18, 1986. Any further recommendations will be forwarded to you.

Sincerely yours,

E. Tabor

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

File → IND

cc: R Nolan
FDA/C.
G T Simpkins

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Adria

ADMINISTRATIVE OFFICES
ADRIA LABORATORIES
Division of Bristol-Myers Inc.
5600 Post Road Dublin Ohio
(614) 764-8100 Telex 246-630
Facsimile (614) 764-8102

January 8, 1987

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Edward Tabor, M.D.
Director
Division of Anti-infective Drug
Products (HFN-815)
Office of Biologic Research & Review
Center for Drugs & Biologics
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NEW IND
Rifabutin

Dear Dr. Tabor:

This is in reference and will confirm Mr. Jim Bona's November 5, 1986 telephone conversation, in which we were requested to establish a new IND to cover the clinical development of rifabutin for antimycobacterial uses currently being developed under IND 27,934.

The current IND will be used for clinical development as an antiviral while the new IND would be devoted to clinical development for antimycobacterial indications.

Enclosed is the new IND. Information concerning preclinical and manufacturing/controls data is by reference to the existing IND. A letter of authorization is included. The IND provides a list of all clinical protocols filed to the existing IND and a copy of the protocol for each antimycobacterial study. The protocol for the MAI study has been included. It should be noted, however, that this protocol has been previously submitted for discussion purposes only. A final protocol will be submitted prior to initiation of the study.

Since this IND is being established for administrative reasons, it was agreed that a 30-day delay waiver would be automatically granted.

Sincerely yours,

Lowell L. Irminger

Lowell L. Irminger
Director Drug Regulatory Affairs,
New Products

LLI/bd
enclosures

MAILING ADDRESS P.O. Box [illegible]

9

Adria
ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc.
5000 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-

January 14, 1987

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Nasim Moledina, M.D.
Division of Anti-infective
Drug Products (HFN-815)
Office of Biologics Research &
Review
Center for Drugs & Biologics
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IND 29-607
Rifabutin
TREATMENT PROTOCOL

Dear Dr. Moledina:

In reference to the above IND and recent telephone discussions
vith R. Nolan, M.D., our Director of Clinical Development,
:oncerning Dr. Thayer's patients with Crohn's disease, we
re submitting the enclosed treatment protocol, an open
ncontrolled study of rifabutin and steptomycin in patients with
evere refractory disease.

r. Thayer, Rhode Island Hospital, is the principal investigator.
is investigator statement and qualifications are enclosed, as
ell as the qualifications of his associate investigators.

beling to be used for study medication is included.

Sincerely yours,

Lowell L. Irminger
Director Drug Regulatory Affairs,
New Products

/bd
losure

G ADDRESS PO Box

ADRIA LABORATORIES

ADRIA LABORATORIES
Division of Erbamont Inc.

P.O. Box 16529
Columbus, OH 43216-6529

January 16, 1992

AIRBORNE

David Feigal, M.D., M.P.H., Director
Division of Antiviral Drug Products (HFD-530)
Food and Drug Administration
Central Document Room 2-14
12420 Parklawn Dr.
Rockville, MD 20852

Re: NDA 50-689
MYCOBUTIN™ (Rifabutin)
Clinical and Statistical, Pharmacokinetics, Microbiology, CMC
New Drug Application

Dear Dr. Feigal:

On behalf of Adria Laboratories and Farmitalia Carlo Erba, it is with great pleasure and excitement that I submit to you the pivotal clinical section of a New Drug Application for Mycobutin™ (rifabutin). I also submit microbiology, pharmacokinetics, and section 4 of Chemistry, Manufacturing, and Controls (CMC). As part of a rolling NDA submission, I previously submitted the toxicology section on October 3, 1991. On November 21, 1991, I sent to the Division the CMC, nonclinical pharmacology and ADME subsections.

A Treatment IND for Mycobutin was submitted on December 30, 1991, and we are prepared to implement the program following the 30-day review. On December 23, 1991, we submitted a formal request for the Division to consider a joint review with the Health Protection Branch (HPB) of Canada. The HPB has agreed to review the submission in the New Drug Application format.

I believe that with this submission, we have met the requirements for a New Drug Application. This submission would not have been possible at this time without the close collaboration, the guidance and expertise of the Antiviral Division staff. We value the Division's input and timely response to questions and concerns presented to your staff during the IND process and filing of the Treatment IND. I am confident your staff will make the review and approval of this application an exciting and expeditious process.

Sincerely yours,

Richard L. Wolgemuth

Richard L. Wolgemuth, Ph.D.
Director Regulatory Affairs, New Drugs

mk
Enclosure

Phone (614) 764-8100 Facsimile (614) 764-8102 Telex 246-620

OVERVIEW

The following summary identifies key events leading to the review of and culminating in the approval of rifabutin by the FDA. It can be seen from this summary and the attachments which follow as a part of this Exhibit 10 the activities of Adria Laboratories in gaining approval of rifabutin were numerous and continuous.

On July 1, 1985 representatives from Adria met with the FDA to discuss the development of rifabutin in the United States.

On February 17, 1986 Adria filed a Notice of Claimed Investigational Exemption for a New Drug which constituted a pre-IND submission. The IND was assigned number 27,934 and was approved on April 18, 1986 following the submission of additional information on April 7, 1986 and waiver by the FDA of the usual 30 day delay.

During 1986 two dose finding studies to investigate rifabutin as an anti-HIV agent were begun. Also, in 1986 a clinical trial in Crohn's disease and a clinical trial in leprosy were filed to IND 27,934.

On July 22, 1986 a meeting was held with the FDA including representatives from CDC to discuss the requirements for studying mycobacterium avium intracellulare complex (MAC) disease. An FDA Advisory Committee discussed rifabutin and clinical endpoints at a meeting on October 20, 1986.

At the request of the FDA, IND 27,934 was restricted to investigations for antiviral indications, and on January 8, 1987, IND 29,607 was assigned for investigations of rifabutin as an antimycobacterial agent.

On November 19, 1987 a meeting was held with representatives of the FDA and CDC to discuss issues relating to the study of pulmonary non-AIDS MAC under IND 29,607 (study initiated October 1988). Numerous dialogue sessions and informal meetings with the Antiviral Drug Products Division were held throughout 1989 to discuss clinical development plans to investigate the prophylaxis of mycobacterial infections in AIDS patients (study initiated January 1990). At an Advisory Committee Meeting held in March of 1990 clinical endpoints to be used for this study were discussed. Communications throughout 1991 were numerous and continuous as is typical for active IND's with ongoing Phase 3 trials. Additionally, a number of pharmacokinetic protocals were submitted as agreed upon with FDA.

In May of 1989 IND 27,934 was withdrawn because the trials did not appear to demonstrate clinical efficacy of rifabutin as an anti-HIV agent.

New Drug Application, NDA 50-689 was submitted on January 16, 1992 for the use of rifabutin for the prevention of mycobacterium avium complex (MAC) infection in HIV positive patients with CD4 cell counts of 200 or less. Approval to market rifabutin for prophylaxis of MAC disease was received from the

FDA on December 23, 1992, as evidenced by the approval letter attached as Exhibit 2.

The attachments which follow comprise a log listing on a daily basis actions taken by Adria and contacts with the FDA beginning prior to the approval (4/18/86) of the first IND (No. 27,934) and ending with the approval of NDA 50-689 on 12/23/92. The log comprises three parts:

IND 27,934	chronology
IND 29,607	chronology
NDA 50-689	chronology

Tabulations setting forth key events occurring during each of the IND phase and the NDA phase are also included.

It is readily apparent from these chronological logs that the activities were numerous and ongoing continuously during the review period reflecting the diligent pursuit by Adria Laboratories of the approval of rifabutin by the FDA.

RIFABUTIN
Division of Anti-Infective Drug Products

Year	IND 27,934	IND 29,607
1986	Investigational New Drug (IND) application filed on 2/17/86 with additional information to complete the IND submitted 4/17/86 Protocols: 087003 - Dose ranging anti-HIV 087004 - Crohn's disease 087005 - Dose tolerance anti-HIV 087007 - Leprosy	
1987	1 Information Amendment included chemistry, manufacturing, and control (CMC) data Annual progress report	New IND established for study of rifabutin as an antimycobacterial agent; cross reference to active IND 27,934; IND 27,934 for study of anti viral indications Protocols: 087008 - Crohn's disease 3 Informations Amendments including clinical and chemistry, manufacturing, and control (CMC) data
1988	4 Information Amendments including CMC, preclinical, clinical data Annual progress report	Protocols: 087011 - Pullmonary MAC infections non-AIDS 3 Information Amendments including CMC, preclinical, clinical data Annual progress report
1989	1 Information Amendment included preclinical, clinical data Annual progress report IND withdrawn	Protocols: 087019 - AZT drug interaction 087023 - Double blind Phase 3 prevention of MAC in AIDS 087039 - AZT drug interaction 6 Information Amendments including CMC, preclinical, clinical data Annual progress report

RIFABUTIN
Division of Anti-Infective Drug Products

Year	IND 27,934	IND 29,607
1990		Protocols: 087027 - Double blind Phase 3 prevention of MAC in AIDS 087032 - Treatment of MAC in AIDS 087040 - Bioavailability and food effect 5 Information Amendments including CMC, preclinical, clinical data Annual progress report
1991		Protocols: 087056 - ddi drug interaction 14 Information Amendments CMC, preclinical, clinical data Annual progress report
1992		Protocols: 087058 - Fluconazole drug interaction 087071 - Methadone drug interaction 087162 - Suspension bioavailability 7 Information Amendments including CMC, preclinical, clinical data Annual progress report

RIFABUTIN (ANTI-VIRAL) IND 27,934 (LM-427)

DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL
03/15/89	014	ANNUAL PROGRESS REPORT	CS# 087005		28
03/15/89	014	ANNUAL PROGRESS REPORT	FREQUENT SERIOUS ADE'S		28
03/15/89	014	ANNUAL PROGRESS REPORT	SAFETY REPORTS		28
03/15/89	014	ANNUAL PROGRESS REPORT	DEATHS ON STUDY		28
03/15/89	014	ANNUAL PROGRESS REPORT	PATIENTS DISCONTINUED		28
03/15/89	014	ANNUAL PROGRESS REPORT	DRUG'S ACTIONS		28
03/15/89	014	ANNUAL PROGRESS REPORT	LIST OF PRECLINICAL STUDIES		28
03/15/89	014	ANNUAL PROGRESS REPORT	MANUFACTURING / MICROBIOLOGICAL		28
03/15/89	014	ANNUAL PROGRESS REPORT	INVESTIGATIONAL PLAN		28
03/15/89	014	ANNUAL PROGRESS REPORT	INVESTIGATORS BROCHURE REVISIONS (NOTHING TO REPORT)		28
03/15/89	014	ANNUAL PROGRESS REPORT	PHASE I PROTOCOL MODIFICATIONS (NOTHING TO REPORT)		28
03/15/89	014	ANNUAL PROGRESS REPORT	FOREIGN MARKETING DEVELOPMENTS (NOTHING TO REPORT)		28
03/15/89	014	ANNUAL PROGRESS REPORT	OUTSTANDING BUSINESS (NOTHING TO REPORT)		28
04/24/89	015	FDA LETTER	INFORMATION ON-HOW TO PROVIDE CLINICAL TRIAL INFORMATION TO AIDS PATIENTS		28
04/25/89	015	WITHDRAWAL OF IND	IND BEING WITHDRAWN - BUT NOT ABANDONED, THEREFORE NOT PUBLICLY DISCLOSABLE		28
05/22/89	015	FDA LETTER	ACKNOWLEDGMENT OF IND WITHDRAWAL REQUEST		28
05/31/89	N/A	LETTER	Response to Paul Parkman to Designate a Person to Serve as a Liaison for Communications about IND 27,934		28

RIFABUTIN (ANTI-VIRAL) IND 27,934 (LM-427)

DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
02/17/89	013	INFO AMENDMENT	Clinical Study No. 087003		28	
02/17/89	013	INFO AMENDMENT	Final Report		28	
02/17/89	013	INFO AMENDMENT	Clinical Study Summary		28	
02/17/89	013	INFO AMENDMENT	Protocol and Amendments		28	
02/17/89	013	INFO AMENDMENT	Data Listings		28	
02/17/89	013	INFO AMENDMENT	Current Clinical Literature Citations		28	
02/17/89	013	INFO AMENDMENT	PHARMACOLOGY		28	
02/17/89	013	INFO AMENDMENT	Pharmacology Detailed Reports (Published)		28	
02/17/89	013	INFO AMENDMENT	AX 0089		28	
02/17/89	013	INFO AMENDMENT	Current Pharmacology Literature Citations		28	
02/17/89	013	INFO AMENDMENT	TOXICOLOGY		28	
02/17/89	013	INFO AMENDMENT	Toxicology Detailed Report (Unpublished)		28	
02/17/89	013	INFO AMENDMENT	428i		28	
03/15/89	014	ANNUAL PROGRESS REPORT	REPORTING PERIOD (2/1/88 - 1/31/89)		28	
03/15/89	014	ANNUAL PROGRESS REPORT	COVER LETTER, 1571 FORM, TABLE OF CONTENTS		28	
03/15/89	014	ANNUAL PROGRESS REPORT	INTRODUCTION		28	
03/15/89	014	ANNUAL PROGRESS REPORT	INDIVIDUAL STUDY INFORMATION		28	
03/15/89	014	ANNUAL PROGRESS REPORT	CS# 087003		28	

RIFABUTIN (ANTI-VIRAL) IND 27,934 (LM-427)

DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
09/08/88	007	INFO AMENDMENT	8D.3. PHARMACOKINETICS (ADME) BIBLIOGRAPHY		26	
09/21/88	008	ADR RPT	MF# 08788003 - FOREIGN - SONIA NATAL RIBEIRO - DEATH DURING STUDY		26	
09/21/88	008	ADR RPT	MF# 08788004 - FOREIGN - SONIA NATAL RIBEIRO - DEATH DURING STUDY		26	
09/21/88	008	ADR RPT	MF# 08788005 - FOREIGN - SONIA NATAL RIBEIRO - VOMITING, NAUSEA AND EPIGASTRIC		26	
09/21/88	008	ADR RPT	PAIN. SUBJECT DIED FIVE DAYS AFTER RIFIBUTIN THERAPY DISCONTINUED		26	
11/14/88	009	INFO AMENDMENT	FINAL REPORT# 87005		27	
11/14/88	009	INFO AMENDMENT	APENDICES		27	
11/14/88	009	INFO AMENDMENT	CLINICAL ABSTRACT AX0110		27	
11/14/88	009	INFO AMENDMENT	STABILITY DATA		27	
11/16/88	010	ADR RPT - FOLLOW-UP	MFR# 08787004 - CS# 870300 - F. SIEGAL - MILD ARTHRALGIA		27	
11/16/88	010	ADR RPT - FOLLOW-UP	MFR# 08787005 - CS# 870300 - F. SIEGAL - POLYARTICULAR ARTHRALGIA W/PERIARTICULAR SWELLING		27	
11/16/88	010	ADR RPT - FOLLOW-UP	MFR# 08787006 - CS# 870300 - F. SIEGAL - POLYARTICULAR ARTHRALGIA W/PERIARTOCULAR SWELLING		27	
01/20/89	011	INFO AMENDMENT	4 RESPONSES TO FDA LETTER 10/11/88 (MFG AND CONTROLS)		27	
02/07/89	012	ADD ASSOCIATE	CS# 087005 - THOMAS C. MERIGAN - 1 ASSOCIATE		27	
02/17/89	013	INFO AMENDMENT	CLINICAL AND PRECLINICAL		28	
02/17/89	013	INFO AMENDMENT	Cover Letter		28	
02/17/89	013	INFO AMENDMENT	FDA Form 1571		28	
02/17/89	013	INFO AMENDMENT	CLINICAL		28	

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DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
05/09/88	005	ANNUAL RPT	Pharmacokinetics/Metabolism	9	26	
05/09/88	005	ANNUAL RPT	Significant Manufacturing or Microbiological Changes Made	7	26	
05/09/88	005	ANNUAL RPT	Investigational Plan	6	26	
05/09/88	005	ANNUAL RPT	Investigational Brochure Revisions (Nothing to Report)	6	26	
05/09/88	005	ANNUAL RPT	Phase I Protocol Modifications (Nothing to Report)	6	26	
05/09/88	005	ANNUAL RPT	Foreign Marketing Developments (Nothing to Report)	6	26	
05/09/88	005	ANNUAL RPT	Log of Outstanding Business (Nothing to Report)	6	26	
06/14/88	006	ADR REPORT	CS# 087003 - MFR# 08788001		26	
09/08/88	007	INFO AMENDMENT	CLINICAL, PHARMACOLOGY, & TOXICOLOGY		26	
09/08/88	007	INFO AMENDMENT	TABLE OF CONTENTS		26	
09/08/88	007	INFO AMENDMENT	4. CLINICAL		26	
09/08/88	007	INFO AMENDMENT	4B. CURRENT BIBLIOGRAPHY		26	
09/08/88	007	INFO AMENDMENT	8. PHARMACOLOGY/TOXICOLOGY		26	
09/08/88	007	INFO AMENDMENT	8A. PHARMACOLOGY DETAILED REPORTS		26	
09/08/88	007	INFO AMENDMENT	8B. TOXICOLOGY DETAILED REPORTS		26	
09/08/88	007	INFO AMENDMENT	8C. PHARMACOKINETICS/METABOLISM DETAILED REPORTS		26	
09/08/88	007	INFO AMENDMENT	8D.1. PHARMACOLOGY BIBLIOGRAPHY		26	
09/08/88	007	INFO AMENDMENT	8D.2. TOXICOLOGY BIBLIOGRAPHY		26	

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DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
04/08/88	004	INFO AMEND	SECT.B - MFG & CTRLS (b) repackaging & labeling bottle & blister	8C	26	
04/08/88	004	INFO AMEND	SECT.B - MFG & CTRLS (c) new HPLC Assay method	8C	26	
04/08/88	004	INFO AMEND	SECT.B - MFG & CTRLS (d) composition,mfg,processing & pkging placebo	8C	26	
04/08/88	004	INFO AMEND	SECT.C - MFG & CTRLS - RIFAMPIN CAPSULES-overencapsulation with orange	8C	26	
05/09/88	005	ANNUAL RPT	Cover Letter, FD Form 1571, Table of Contents		26	
05/09/88	005	ANNUAL RPT	Individual Study Information	6	26	
05/09/88	005	ANNUAL RPT	Introduction	6	26	
05/09/88	005	ANNUAL RPT	Brief Summary of Studies in Progress or Completed (4-1-87 - 1-31-88)	6	26	
05/09/88	005	ANNUAL RPT	CS# 087003	6	26	
05/09/88	005	ANNUAL RPT	CS# 087005	6	26	
05/09/88	005	ANNUAL RPT	Summary Information	6	26	
05/09/88	005	ANNUAL RPT	Summary of Most Frequent and Most Serious Adverse Experiences -	6	26	
05/09/88	005	ANNUAL RPT	Summary of Safety Reports Submitted 4/1/87 - 1/31/88	6	26	
05/09/88	005	ANNUAL RPT	List of Patients Who Died "On-Study" 4/1/87 - 1/31/88	6	26	
05/09/88	005	ANNUAL RPT	List of Patients Discontinued Toxicity/Adverse Reaction or Patient Refusal	6	26	
05/09/88	005	ANNUAL RPT	Information Obtained Pertinent to an Understanding of the Drug's Actions	6	26	
05/09/88	005	ANNUAL RPT	List of Preclinical Studies	8	26	
05/09/88	005	ANNUAL RPT	Pharmacology	8	26	

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03/11/88	003	INFO AMEND	Cover Letter, FORM 1571, TABLE OF CONTENTS		25	
03/11/88	003	INFO AMEND	PHARMACOLOGY/TOXICOLOGY	8	25	
03/11/88	003	INFO AMEND	PHARMACOLOGY	8A	25	
03/11/88	003	INFO AMEND	Detailed Reports - 214i, 217i, 218i, 219i	8A	25	
03/11/88	003	INFO AMEND	PHARMACOKINETICS/METABOLISM	8B	25	
03/11/88	003	INFO AMEND	Detailed Reports - 609i, 610i, 802i, 803i, 811i	8B	25	
03/11/88	003	INFO AMEND	Detailed Reports (cont.) - 812i, 813i, 814i, 815i, 816i	8B	25	
03/11/88	003	INFO AMEND	Detailed Reports (cont.) - 817i, AX0047, AX0061	8B	25	
03/11/88	003	INFO AMEND	1.PHARMACOLOGY BIBLIOGRAPHY	8C(1)	25	
03/11/88	003	INFO AMEND	2.PHARMACOKINETIC (ADME) BIBLIOGRAPHY	8C(2)	25	
04/08/88	004	INFO AMEND	SECT.A - RESPONSE 1 -metobolic studies needed in animals	8A	26	
04/08/88	004	INFO AMEND	SECT.A - RESPONSE 2 -need toxicity data for dose levels above 450mg	8B	26	
04/08/88	004	INFO AMEND	SECT.A - RESPONSE 3 -interim results for mouse & rat CA studies	8B	26	
04/08/88	004	INFO AMEND	SECT.A - RESPONSE 4 -results of 1 yr. rat study needed	8B	26	
04/08/88	004	INFO AMEND	SECT.A - RESPONSE 5 -Heinz Bodiy formation	8B	26	
04/08/88	004	INFO AMEND	SECT.A - RESPONSE 6 -alternate-day administration	8B	26	
04/08/88	004	INFO AMEND	SECT.A - RESPONSE 7 -"Arneth's count"	8B	26	
04/08/88	004	INFO AMEND	SECT.B - MFG & CTRLS (a) use Swedish orange capsules	8C	26	

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DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
07/28/87		ANNUAL RPT	DETAILED REPORTS	VOL 1-6	19-24	
07/28/87		ANNUAL RPT	SUMMARY TABLES	VOL 1-6	19-24	
07/28/87		ANNUAL RPT	TOXICOLOGY	VOL 1-6	19-24	
07/28/87		ANNUAL RPT	DETAILED REPORTS	VOL 1	24	
07/28/87		ANNUAL RPT	SUMMARY TABLES	VOL 1	24	
07/28/87		ANNUAL RPT	PHARMACOLOGY	VOL 1	24	
07/28/87		ANNUAL RPT	DISSOLUTION PROCEDURES AND STABILITY SUMMARY	VOL 1	24	
07/28/87		ANNUAL RPT	MANUFACTURING AND CONTROLS	VOL 1	24	
07/28/87		ANNUAL RPT	LITERATURE CITATIONS AND ABSTRACTS	VOL 1	24	
07/28/87		ANNUAL RPT	LIST OF REPORTS	VOL 1	24	
07/28/87		ANNUAL RPT	STATUS OF U.S.STUDIES	VOL 1	24	
07/28/87		ANNUAL RPT	CLINICAL CUMULATIVE INVESTIGATOR LIST	VOL 1	24	
07/28/87		ANNUAL RPT	INDEX	VOL 1	24	
08/05/87		PROTO AMEND	REV PROTOCOL - DR. SIEGAL - PERTAINING TO DOSE ESCALATION		24	
09/25/87	001	ADR REPORT	MFR# 08787004 /CS# 870300 /Dr.SIEGAL /MILD ARTHRALGIA		24	
09/25/87	001	ADR REPORT	MFR# 08787005 /CS# 870300 /Dr.SIEGAL /POLYARTICULAR ARTHRALGIA		24	
09/25/87	001	ADR REPORT	MFR# 08787006 /CS# 870300 /Dr.SIEGAL /POLYARTICULAR ARTHRALGIA		24	
01/26/88	002	ADR REPORT	MFR# 08788001 / CS# 087003 / Dr. SIEGAL / UVEITIS		24	

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DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
01/08/87		LETTER TO FDA	LETTER OF AUTHORIZATION TO REFERENCE IND 27,934 TO IND 27,607		17	
01/15/87		REV PROTOCOL	CS# 087003 - FREDERICK SIEGAL (AMENDMENT DATED 12/16/86)		17	
01/27/87		REV PROTOCOL	CS# 087005 - THOMAS MERIGAN -(AMENDMENT DATED 1/6/87) - 600mg/DAY TO 900mg/DAY		17	
03/12/87		LETTER FROM FDA	REFER MEETING 7/22/86 CONCERNING RIFABUTIN FOR TREATMENT OF MYCOBACTERIUM AVIUM INTRACELLULARE		17	
03/13/87		LETTER TO FDA	REFERENCE TO REV PROTOCOL 087003 CHANGE IN PATIENTS/DOSE LEVEL AND CHANGE IN DURATION		17	
03/27/87		REV PROTOCOL (RESUMITTED)	PROTOCOL 087007 RESUMITTED TO EDWARD TABOR		17	
04/10/87		LETTER TO FDA	AUTHORIZATION GRANTED TO ENTER 14 YEAR OLD BOY TO CS# 8703 - TELEPHONE CONVERSATION OF 3/19/87		17	
05/20/87		LETTER TO FDA	RESPONSE TO 10/15/86 LETTER REQUESTING ADDITIONAL INFORMATION		18	
05/20/87		LETTER TO FDA	HIV ASSAY PROCEDURE - STANFORD UNIVERSITY		18	
05/20/87		LETTER TO FDA	HIV ASSAY PROCEDURE - SUNY AT STONY BROOK		18	
05/20/87		LETTER TO FDA	CS# 087005 - 1/23/87 - PROTOCOL AMENDMENT		18	
05/20/87		LETTER TO FDA	CS# 087005 - 9/23/86 - PROTOCOL AMENDMENT		18	
05/20/87		LETTER TO FDA	CS# 087003 - 11/19/86 - COVER LETTER - PROTOCOL AMENDMENT		18	
05/23/87		AMENDMENT	CHEMISTRY,MFG/CONTROLS - CHANGE IN SPECIFICATIONS AND TEST METHODS		18	
07/02/87		CHG CLIN MONITOR	CLINICAL MONITOR: MARGARET REAL,M.D., ASSOCIATE MONITOR: BEVERLY WYNN		18	
07/15/87		ADR REPORT	MFR#08787001 CS# FOREIGN /THROMBOCYTOPENIA-INTRACEREBRAL HEMORRHAGE		18	
07/28/87		ADR REPORT	MFR#08787003 CS# FOREIGN /FEVER,MALAISE,MYALGIA,ARTHRALGIA		18	
07/28/87		ANNUAL RPT	PHARMACOKINETICS	VOL 6	19	

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DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
07/03/86		AMENDMENT TO IND	LTR TO SET UP MEETING RE:CLINICAL DEVELOPMENT PLAN FOR A NEW PROTOCOL (PULMONARY MAC DIEASE)		16	
07/11/86		PROTOCOL AMENDMENT	PROTOCOL AMENDMENT CS# 087003 - Dr. SIEGAL (AMENDMENT TO PROTOCOL DATED 3/11/86)		16	
07/11/86		PROTOCOL AMENDMENT	PROTOCOL AMENDMENT CS# 087003 - Dr. SIEGAL (AMENDMENT TO PROTOCOL DATED 4/22/86)		16	
07/17/86		NEW CLIN STDY	NEW STUDY CS# 087005 - THOMAS MERIGAN,M.D.		16	
07/23/86		SIEGAL's IND	ADR REPORT FROM Dr.SIEGAL TO E.COOPER AT THE FDA ON HIS IND 26,969		16	
08/01/86		LTR	PATIENT CONSENT FORM AND CASE REPORT FORMS FOR DR. FREDERICK SIEGAL (CS# 087003)		16	
08/13/86		LETTER FROM FDA	RE: REQUEST FOR MORE DATA ON IN VITRO & MFG/CTRLS BEFORE PHASE III STUDIES ARE INITIATED		16	
08/19/86		NEW CLIN STDY	CS# 087004 - WALTER THAYER - "SEVERE CROHN'S DISEASE"		16	
08/22/86		LETTER FROM FDA	RECOMMENDATIONS AND COMMENTS FOR PRECLINICAL STUDIES SUBMITTED ON 2/17/86		16	
09/05/86		ADD ASSOC INV	CS# 087003 - Dr.SIEGAL (ASSOC. INV : EILBOTT,JAGATHAMBAL,REIFE,GEHAN,SINGER)		17	
09/11/86		LETTER TO FDA	RESPONCE TO LETTER FROM FDA DATED 8/13/86 : INFO ALREADY SUBMITTED		17	
09/23/86		PROTOCOL AMENDMENT	PROTOCOL AMENDMENT FOR MERIGAN STUDY - CS# 87005-000		17	
10/18/86		AMENDMENT RADIOLABELED STUDY	REFERENCE TO TELEPHONE REQUEST CONCERNING MERIGAN STUDY (10/16/86)		17	
10/20/86		NEW CLIN STDY	CS# 087007 -ROBERT JACOBSON - "MYCOBACTERIUM LEPRAE"		17	
10/20/86		REPORT FOR A MEETING	Dr. MICHAEL ISEMAN'S REPORT TO THE ANTIINFECTIVE ADVISORY COMMITTEE		17	
11/19/86		REV PROTOCOL	REV PROTOCOL CS# 087003 - Dr. SIEGAL (AMENDMENT TO PROTOCOL DATED 10/23/86)		17	
11/19/86		PATIENT CONSENT FORMS	CS# 087007 - ROBERT JACOBSEN (PATIENT CONSENT FORMS		17	
01/06/87		LETTER FROM FDA	PROTOCOL 087004 NOT APPROVED AT THIS TIME		17	

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DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
04/07/86		IND SUBM (CLINICAL)	SECTION 6C (COMBINATION DRUG STATEMENT)	7	14	
04/07/86		IND SUBM (CLINICAL)	SECTION 7 (INFORMATION MATERIAL)	7	15	
04/07/86		IND SUBM (CLINICAL)	CLINICAL BROCHURE	7	15	
04/07/86		IND SUBM (CLINICAL)	PRODUCT LABELING	8	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 8 (STATEMENT OF QUALIFICATIONS)	9	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 9 (CURRICULUM VITAE)	9	15	
04/07/86		IND SUBM (CLINICAL)	CLINICAL MONITOR (ADRIA MONITOR - ROBERT NOLAN)	8	15	
04/07/86		IND SUBM (CLINICAL)	CLINICAL INVESTIGATOR (087003 - FREDERICK SIEGAL)	10	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 10 (OUTLINE OF ANY PHASES OF PLANNED INVESTIGATIONS)	10	15	
04/07/86		IND SUBM (CLINICAL)	PROTOCOL CS# 087003 - FREDERICK SIEGAL	11	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 11 (FDA NOTIFICATION STATEMENT)	12	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 12 (INVESTIGATORS NOTIFICATION STATEMENT)	13	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 13 (NON-COMMERCIALIZATION STATEMENT)	14	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 14 (30-DAY DELAY OR WAIVER STATEMENT)	15	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 15 (ENVIRONMENTAL IMPACT ANALYSIS)	16	15	
04/07/86		IND SUBM (CLINICAL)	SECTION 16 (CONFORMING ANALYSIS STATEMENT)		15	
04/16/86		AUTHORIZATION	LETTER APPOINTING ADRIA LABORATORIES AS U.S. AGENT FOR FARMITALIA' DFM 4882		16	
06/02/86		LETTER FROM FDA	"PROCEED W/ STUDY" LTR FOR Dr. SIEGAL , PROTOCOL CS# 087003		16	

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DATE	SER.	TYPE SUBMISSION	LETTER SUBJECT	SEC	VOL	FICHE #
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	SUBACUTE TOXICOLOGY REPORTS	6	4-8	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	CHRONIC TOXICITY	6	9-11	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	ORGANOGENESIS		12	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	MUTAGENESIS		13	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	CYTOTOXICITY		13	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	APPENDIX I		13	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	APPENDIX II		13	
02/24/86		FDA	LETTER ACKNOWLEDGES RECEIPT OF PRE-IND SUBMISSION DATED 2/17/86		14	
04/07/86		IND SUBM (CLINICAL)	SECTION 1-5 (DESCRIPTION OF DRUG)	1	14	
04/07/86		IND SUBM (CLINICAL)	SECTION 1-5 (COMPONENTS)	2	14	
04/07/86		IND SUBM (CLINICAL)	SECTION 1-5 (COMPOSITION)	3	14	
04/07/86		IND SUBM (CLINICAL)	SECTION 1-5 (SYNTHESIS OF ADS)	3	14	
04/07/86		IND SUBM (CLINICAL)	SECTION 1-5 (MFG/CTRLS)	5	14	
04/07/86		IND SUBM (CLINICAL)	SECTION 6B (FOREIGN INVESTIGATIONS)	6	14	
04/07/86		IND SUBM (CLINICAL)	CLINICAL SUMMARY	10A	14	
04/07/86		IND SUBM (CLINICAL)	TABLES	10B	14	
04/07/86		IND SUBM (CLINICAL)	REFERNECES (INDEX)	10B	14	
04/07/86		IND SUBM (CLINICAL)	REFERENCES (REPORTS)	10B	14	

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02/17/86		PRE-IND SUBM (PRE-CLINICAL)	FORM FD 1571		1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	CLINICAL OVERVIEW	10B	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	GLP CONFORMING AMENDMENTS	16	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	SECTION 6	6	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	SECTION 6A	6A	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	CURRICULA VITAE	8	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	PHARMACOLOGY (TABLE OF CONTENTS)	6	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	PHARMACOLOGY OVERVIEW	6A	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	IN VITRO ACTIVITY	6B	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	PHARMACOLOGY	6	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	PHARMACOLOGY SUMMARY TABLE	6A	1	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	PHARMACOLOGY DETAILED REPORTS	6C	1&2	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	TOXICOLOGY (TABLE OF CONTENTS)	6	3	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	TOXICOLOGY OVERVIEW	6A	3	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	TOXICOLOGY SUMMARY TABLE	6A	3	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	TOXICOLOGY DATAILED REPORTS	6C	3	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	ACUTE TOXICOLOGY REPORTS	6	3	
02/17/86		PRE-IND SUBM (PRE-CLINICAL)	SUBACUTE TOXICOLOGY REPORTS	6	3	

RIFABUTIN (ANTI-MYCOBACTERIAL) - IND 29,607 (LM-427)

DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
05/02/91	116	INFORMATION AMENDMENT	FINAL REPORT - CS# 087054-000 - FARMITALIA STUDY AU87610	42
05/02/91	116	INFORMATION AMENDMENT	TABLE OF CONTENTS	42
05/02/91	116	INFORMATION AMENDMENT	SYNOPSIS	42
05/02/91	116	INFORMATION AMENDMENT	1.0 INTRODUCTION	42
05/02/91	116	INFORMATION AMENDMENT	2.0 OBJECTIVE	42
05/02/91	116	INFORMATION AMENDMENT	3.0 STUDY DESIGN	42
05/02/91	116	INFORMATION AMENDMENT	4.0 DATA QUALITY	42
05/02/91	116	INFORMATION AMENDMENT	5.0 STATISTICAL METHODS	42
05/02/91	116	INFORMATION AMENDMENT	6.0 RESULTS	42
05/02/91	116	INFORMATION AMENDMENT	7.0 DISCUSSION	42
05/02/91	116	INFORMATION AMENDMENT	8.0 REFERENCES	42
05/02/91	116	INFORMATION AMENDMENT	TABLES	42
05/02/91	116	INFORMATION AMENDMENT	FIGURES	42
05/02/91	116	INFORMATION AMENDMENT	TABLE OF CONTENTS FOR APPENDICES A-U PLUS ALL THE APPENDICES	42
05/02/91	116	INFORMATION AMENDMENT	PUBLISHED REPORT# AX 0196	42
05/06/91	117	REVISED PROTOCOL	CS# 087027-999 - Rifabutin available for MAC during trial - Update registering patients	43
05/06/91	117	REVISED PROTOCOL	& Processing Plasma Samples	43
05/08/91	118	UPDATE 1572	CS# 087023-009 - BERNARD BIHARI - DRUG SHIPMENT ADDRESS	43

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
05/01/91	114	INFORMATION AMENDMENT	APPENDICES N-O	35
05/01/91	114	INFORMATION AMENDMENT	FINAL REPORT CS# 087044-999 - CDC	34
05/01/91	114	INFORMATION AMENDMENT	TABLE OF CONTENTS	34
05/01/91	114	INFORMATION AMENDMENT	SYNOPSIS	34
05/01/91	114	INFORMATION AMENDMENT	1.0 INTRODUCTION	34
05/01/91	114	INFORMATION AMENDMENT	2.0 OBJECTIVE	34
05/01/91	114	INFORMATION AMENDMENT	3.0 STUDY DESIGN	34
05/01/91	114	INFORMATION AMENDMENT	4.0 DATA QUALITY	34
05/01/91	114	INFORMATION AMENDMENT	5.0 STATISTICAL METHODS	34
05/01/91	114	INFORMATION AMENDMENT	6.0 RESULTS	34
05/01/91	114	INFORMATION AMENDMENT	7.0 DISCUSSION	34
05/01/91	114	INFORMATION AMENDMENT	8.0 REFERENCES	34
05/01/91	114	INFORMATION AMENDMENT	TABLES	34
05/01/91	114	INFORMATION AMENDMENT	FIGURES	34
05/01/91	114	INFORMATION AMENDMENT	APPENDICES A-F	33
05/01/91	114	INFORMATION AMENDMENT	APPENDICES G-L	32
05/01/91	114	INFORMATION AMENDMENT	APPENDICES M-P	31
05/02/91	116	INFORMATION AMENDMENT	CLINICAL	42

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	
05/01/91	114	INFORMATION AMENDMENT	FINAL REPORT CS# 087043-999 - CDC	
05/01/91	114	INFORMATION AMENDMENT	TABLE OF CONTENTS	
05/01/91	114	INFORMATION AMENDMENT	SYNOPSIS	41
05/01/91	114	INFORMATION AMENDMENT	1.0 INTRODUCTION	4
05/01/91	114	INFORMATION AMENDMENT	2.0 OBJECTIVE	4
05/01/91	114	INFORMATION AMENDMENT	3.0 STUDY DESIGN	41
05/01/91	114	INFORMATION AMENDMENT	4.0 DATA QUALITY	41
05/01/91	114	INFORMATION AMENDMENT	5.0 STATISTICAL METHODS	41
05/01/91	114	INFORMATION AMENDMENT	6.0 RESULTS	41
05/01/91	114	INFORMATION AMENDMENT	7.0 DISCUSSION	41
05/01/91	114	INFORMATION AMENDMENT	8.0 REFERENCES	41
05/01/91	114	INFORMATION AMENDMENT	TABLES	41
05/01/91	114	INFORMATION AMENDMENT	FIGURES	41
05/01/91	114	INFORMATION AMENDMENT	APPENDICES A-E	40
05/01/91	114	INFORMATION AMENDMENT	APPENDICES F-H	39
05/01/91	114	INFORMATION AMENDMENT	APPENDICES I-K	38
05/01/91	114	INFORMATION AMENDMENT	APPENDICES L	37
05/01/91	114	INFORMATION AMENDMENT	APPENDICES M	36

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
04/30/91	115	UPDATED 1572	CS# 087023-031 - AMIAD NAJJAR	30
04/30/91	115	UPDATED 1572	CS# 087023-038 - ANTHONY LAMARCA	30
04/30/91	115	UPDATED 1572	CS# 087023-041 - NELSON ZIDE	30
04/30/91	115	UPDATED 1572	CS# 087023-046 - PAUL CIMOCH	30
04/30/91	115	UPDATED 1572	CS# 087027-001 - STANLEY DERESINSKI	30
04/30/91	115	UPDATED 1572	CS# 087027-007 - DAVID FEIGAL	30
04/30/91	115	UPDATED 1572	CS# 087027-008 - SANDY POMERANTZ	30
04/30/91	115	UPDATED 1572	CS# 087027-009 - PAULA SPARTI	30
04/30/91	115	UPDATED 1572	CS# 087027-013 - C. LYNN BESCH	30
04/30/91	115	UPDATED 1572	CS# 087027-016 - DONALD ROMIG	30
04/30/91	115	UPDATED 1572	CS# 087027-017 - LAWRENCE CRANE	30
04/30/91	115	UPDATED 1572	CS# 087027-022 - ROBERTA LUSKIN	30
04/30/91	115	UPDATED 1572	CS# 087027-025 - STEVEN SCHEIBEL	30
04/30/91	115	UPDATED 1572	CS# 087027-026 - LINDA L. CROCKER-SMITH	30
04/30/91	115	UPDATED 1572	CS# 087027-030 - GREGORY MERTZ	30
04/30/91	115	UPDATED 1572	CS# 087027-033 - JOHN P. PHAIR	30
04/30/91	115	UPDATED 1572	CS# 087027-034 - NANCY G. KLIMAS	30
05/01/91	114	INFORMATION AMENDMENT	CLINICAL	31-41

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
04/18/91	112	ANNUAL PROGRESS REPORT	List of Subjects Discontinued in Association with an Adverse Reaction	30
04/18/91	112	ANNUAL PROGRESS REPORT	Information Obtained Pertinent to an Understanding of the Drug's Actions	30
04/18/91	112	ANNUAL PROGRESS REPORT	List of Preclinical Studies	30
04/18/91	112	ANNUAL PROGRESS REPORT	Pharm. Sum. Tables, ADME Sum. Tables, Toxicology Sum. Tables	30
04/18/91	112	ANNUAL PROGRESS REPORT	Significant Mfg. or Microbiological Changes Made During the Past Year	30
04/18/91	112	ANNUAL PROGRESS REPORT	Investigational Plan	30
04/18/91	112	ANNUAL PROGRESS REPORT	Investigational Brochure Revisions	30
04/18/91	112	ANNUAL PROGRESS REPORT	Phase I Protocol Modifications	30
04/18/91	112	ANNUAL PROGRESS REPORT	Foreign Marketing Developments	30
04/18/91	112	ANNUAL PROGRESS REPORT	Log of Outstanding Business	30
04/19/91	113	ADR REPORT	MFR# 08791023 - CS# 087023-007 - GRAND MAL SEIZURES	30
04/30/91	115	UPDATED 1572	CS# 087023-001 - STEVEN D. NIGHTINGALE	30
04/30/91	115	UPDATED 1572	CS# 087023-005 - SUSAN MILLER	30
04/30/91	115	UPDATED 1572	CS# 087023-006 - MICHAEL F. PARA	30
04/30/91	115	UPDATED 1572	CS# 087023-007 - WILLIAM REITER	30
04/30/91	115	UPDATED 1572	CS# 087023-009 - BERNARD BIHARI	30
04/30/91	115	UPDATED 1572	CS# 087023-015 - RICHARD W. CHAISSON	30
04/30/91	115	UPDATED 1572	CS# 087023-020 - EARL MATTHEW	30

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
04/12/91	108	ADD ASSOCIATE	CS# 087027-033 - JOHN P. PHAIR - ADD 1 ASSOCIATE	29
04/12/91	108	CHANGE OF ADDRESS	CS# 087027-034 - NANCY G. KLIMAS - NEW ADDRESS	29
04/12/91	109	ADR REPORT	CS# 087027-018 - MFR# 08791019 - Seizure preceded by syncope	29
04/12/91	109	ADR REPORT	CS# 087027-009 - MFR# 08791020 - Grand mal seizure with unconsciousness	29
04/15/91	110	PROTOCOL AMENDMENT	LABELS FOR CS# 087065-999	29
04/15/91	110	NEW INVESTIGATOR	CS# 087065-004 - ALFRED F. BURNSIDE, JR. - 0 ASSOCIATES	29
04/17/91	111	REVISED PROTOCOL	CS# 087056-000 Amendment # 1 (03/19/91) (Draft Protocol Submitted 03/05/91, Serial# 101)	30
04/17/91	111	NEW CLINICAL STUDY	1571 Form - D. William Cameron, M.D.	30
04/17/91	111	NEW CLINICAL STUDY	Curricula Vitae - CS# 087056-000 (W. Cameron and 3 Associates)	30
04/17/91	111	NEW CLINICAL STUDY	Labels - 150mg/Capsules (68 Capsules per Patient)	30
04/18/91	112	ANNUAL PROGRESS REPORT	Cover Letter, FDA Form 1571, Table of Contents (01/01/90 - 12/31/90)	30
04/18/91	112	ANNUAL PROGRESS REPORT	Study Information	30
04/18/91	112	ANNUAL PROGRESS REPORT	Introduction	30
04/18/91	112	ANNUAL PROGRESS REPORT	Individual Study Information in progress or completed	30
04/18/91	112	ANNUAL PROGRESS REPORT	Summary Information	30
04/18/91	112	ANNUAL PROGRESS REPORT	Summary of Adverse Experiences	30
04/18/91	112	ANNUAL PROGRESS REPORT	Summary of Safety Reports Submitted	30
04/18/91	112	ANNUAL PROGRESS REPORT	List of Subjects Who Died "On/Off Study"	30

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
03/12/91	104	CHANGE OF P.I.	CS# 087023-025 - F. KEVIN MURPHY - 1 ASSOCIATE	29
03/27/91	105	GENERAL CORRESPONDENCE	LETTER TO CASPI - CS# 087065-999 HAS BEEN INITIATED (AIDS RELATED CLINICAL TRIAL)	29
04/05/91	107	ADR REPORT	MFR# 08791013 - CS# 087023-023 - THROMBOTIC THROMBOCYTOPENIC PURPURA	29
04/09/91	106	INFORMATION AMENDMENT	Stability Summary	29
04/09/91	106	INFORMATION AMENDMENT	a. Rifabutin Capsules	29
04/09/91	106	INFORMATION AMENDMENT	b. Over-encapsulated Rifampin Capsules	29
04/09/91	106	INFORMATION AMENDMENT	c. Rifabutin Oral Solution	29
04/12/91	108	NEW INVESIGATOR	CS# 087027-036 - STEPHEN HALL - 2 ASSOCIATES	29
04/12/91	108	NEW INVESIGATOR	CS# 087027-509 - RICHARD LALONDE - 6 ASSOCIATES	29
04/12/91	108	NEW INVESIGATOR	CS# 087027-511 - JULIO MONTANER - 4 ASSOCIATES	29
04/12/91	108	CHANGE OF ADDRESS	CS# 087023-009 - BERNARD BIHARI - NEW ADDRESS & DRUG SHIPMENT ADDRESS	29
04/12/91	108	ADD ASSOCIATE	CS# 087023-009 - BERNARD BIHARI - 1 ASSOCIATE	29
04/12/91	108	DRUG SHIPIMENT ADDRESS	CS# 087023-015 - RICHARD E. CHAISSON - NEW DRUG SHIPMENT ADDRESS	29
04/12/91	108	CHANGE OF ADDRESS	CS# 087027-008 - SANDY POMERANTZ - NEW ADDRESS	29
04/12/91	108	DELETE ASSOCIATE	CS# 087027-008 - SANDY POMERANTZ - DELETE 1 ASSOCIATE	29
04/12/91	108	ADD ASSOCIATE	CS# 087027-009 - PAULA SPARTI - 2 ASSOCIATES	29
04/12/91	108	ADD ASSOCIATE	CS# 087027-022 - ROBERTA LUSKIN - 3 ASSOCIATES	29
04/12/91	108	DRUG SHIPMENT ADDRESS	CS# 087027-033 - JOHN P. PHAIR - NEW DRUG SHIPMENT ADDRESS	29

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
02/11/91	098	REVISED PROTOCOL	CS# 087027-999 - CANADIAN PROTOCOL - AMENDMENT #1 - OCTOBER 30, 1990	27
02/14/91	099	NEW INVESTIGATOR	CS# 087027-501 - STEPHEN D. SHAFRAN - 9 ASSOCIATES	28
02/14/91	099	NEW INVESTIGATOR	CS# 087027-502 - WALTER SCHLECH - 0 ASSOCIATES	28
02/14/91	099	NEW INVESTIGATOR	CS# 087027-503 - WILLIAM CAMERON - 2 ASSOCIATES	28
02/14/91	099	NEW INVESTIGATOR	CS# 087027-507 - FIONA SMAILL - 3 ASSOCIATES	28
02/14/91	099	NEW INVESTIGATOR	CS# 087027-508 - MARK MILLER - 2 ASSOCIATES	28
02/14/91	099	NEW INVESTIGATOR	CS# 087027-510 - JOHN GILL - 1 ASSOCIATE	28
03/05/91	100	ADR REPORT - FOLLOW-UP	MFR# 08790033 - Foreign - Dr. Lucas - Victoria, Australia - Death/Septicemia/AIDS/Pancytopenia	28
03/05/91	101	NEW CLINICAL STUDY	CS# 087056-000 - Phase I Steady-State, Pharmacokinetics & Safety Drug Interaction Study	28
03/06/91	102	ADR REPORT	MFR# 08791009 - CS# 087027-018 - John Stern - Death (Unobserved)	28
03/07/91	103	INFORMATION AMENDMENT	Summary of ADR Reports (Deaths) for CS# 087023 and CS# 087027 as of 01/30/91	28
03/12/91	104	NEW INVESTIGATOR	CS# 087023-026 - SCOTT LEA - 2 ASSOCIATES	29
03/12/91	104	NEW INVESTIGATOR	CS# 087023-037 - JOHN CAREY - 0 ASSOCIATES	29
03/12/91	104	NEW INVESTIGATOR	CS# 087023-042 - CAL COHEN - 13 ASSOCIATES	29
03/12/91	104	NEW INVESTIGATOR	CS# 087027-038 - CAROL BROSGART - 2 ASSOCIATES	29
03/12/91	104	NEW INVESTIGATOR (CANADA)	CS# 087027-504 - EMIL TOMA - 1 ASSOCIATE	29
03/12/91	104	UPDATED 1572 FORM	CS# 0876011-031 - KESAVAN KUTTY - ADD FACILITY	29
03/12/91	104	UPDATED 1572 FORM	CS# 0870213-028 - JEAN A. SMITH - 1 ASSOCIATE - ADD LABORATORIES - DELETE LABORATORY	29

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
01/04/91	092	ADR REPORT	MFR# 08790033 - Foreign - Dr. Ron Lucas - Victoria, Australia - Death/Septicemia/AIDS/Pancytopenia	27
01/04/91	092	ADR REPORT	MFR# 08790034 - Foreign - Dr. Dedivitis Franco - Milan, Italy - Partial Intestinal Obstruction	27
01/04/91	092	ADR REPORT	MFR# 08790035 - CS# 087023-004 - David Kaufman - Right Visual Field Loss	27
01/21/91	093	ADR REPORT - FOREIGN	MFR# 08791001 - DR. G. NICOLET-CHATELAIN - GENEVE, SWITZERLAND - TOXIC HEPATITIS	27
01/22/91	094	ADR REPORT - FOLLOWUP/FOREIGN	MFR# 08790012 - DR. POGGONSEE - BERLIN, FGR - DEPRESSION (AGGRAVATED), PSYCHOSIS	27
01/24/91	095	ADR REPORT - (3-DAY)	MFR# 08791003 - CS# 087023-001 - DEATH, HEPATIC COMA, HEPATITIS, PANCREATITIS	27
01/31/91	096	ADD &/OR DELETE ASSOCIATES	CS# 087023-006 - MICHAEL F. PARA - ADD 3 ASSOCIATES - DELETE 3 ASSOCIATES	27
01/31/91	096	ADD &/OR DELETE ASSOCIATES	CS# 087027-001 - STANLEY C. DERESINSKI - ADD 5 ASSOCIATES	27
01/31/91	096	CHANGE MD TO DO	CS# 087027-019 - CHANGE STEPHEN HAUPTMAN FROM A M.D. TO A D.O.	27
01/31/91	096	CHANGE P.I. & ADD ASSOC.	CS# 087023-007 - WILLIAM REITER - 1 ASSOCIATE	27
01/31/91	096	NEW INVESTIGATOR	CS# 087023-002 - DON ARMSTRONG - 0 ASSOCIATES	27
01/31/91	096	NEW INVESTIGATOR	CS# 087023-034 - AARON GLATT - 4 ASSOCIATES	27
01/31/91	096	NEW INVESTIGATOR	CS# 087023-044 - LARRY I. LUTWICK - 2 ASSOCIATES	27
01/31/91	096	NEW INVESTIGATOR	CS# 087023-046 - PAUL CIMOCH - 0 ASSOCIATES	27
01/31/91	096	NEW INVESTIGATOR	CS# 087027-032 - LARRY A. WAITES - 1 ASSOCIATE	27
02/05/91	097	ADR REPORT	MFR# 08791005 - CS# 087027-008 - S. POMERANTZ - GRADE IV NEUTROPENIA, LIVER DYSFUNCTION	27
02/11/91	098	REVISED PROTOCOL	CS# 087025-999 - JANUARY 17, 1991 - PREVIOUSLY SUBMITTED AS SERIAL# 043 & 068	27
02/11/91	098	NEW PROTOCOL	CS# 087065-999 - JANUARY 20, 1991	27

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
11/19/90	087	NEW INVESTIGATOR	CS# 087023-029 - LAUREN HOSBRATSCH - 1 ASSOCIATE	26
11/19/90	087	NEW INVESTIGATOR	CS# 087023-035 - LAWRENCE DALL - 2 ASSOCIATES	26
11/19/90	087	NEW INVESTIGATOR	CS# 087027-031 - FRANK RHAME - 0 ASSOCIATES	26
11/19/90	087	NEW INVESTIGATOR	CS# 087027-034 - NANCY KLIMAS - 2 ASSOCIATES	26
12/03/90	088	ADR REPORT	MFR# 08790031 - CS# 087027-004 - GRADE IV NEUTROPENIA	26
12/10/90	089	GENERAL CORRESPONDENCE	CROSS REFERENCE IND WITH WALTER THAYER, M.D. - CROHN'S DISEASE	26
12/10/90	090	ADR REPORT	MFR# 08790032 - CS# 087027-026 - L. Lou Smith - Agranulocytosis	26
12/17/90	091	CHANGE OF ADDRESS	CS# 087023-020 - EARL MATTHEW - 0 ASSOCIATES	27
12/17/90	091	NEW INVESTIGATOR	CS# 087023-041 - NELSON ZIDE - 1 ASSOCIATE	27
12/17/90	091	NEW INVESTIGATOR	CS# 087027-030 - GREGORY MERTZ - 4 ASSOCIATES	27
12/17/90	091	NEW INVESTIGATOR	CS# 087027-035 - KEITH HENRY - 1 ASSOCIATE	27

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
10/30/90	081	INFORMATION AMENDMENT	CLINICAL INFORMATION	25
10/30/90	081	INFORMATION AMENDMENT	REVISED INVESTIGATORS BROCHURE (REVISED OCTOBER, 1990)	25
10/30/90	081	INFORMATION AMENDMENT	LITERATURE UPDATE (OCTOBER 2, 1990)	25
11/01/90	082	REVISED PROTOCOL	CS# 087023-999 - AMENDMENT # 2 (OCTOBER 22, 1990)	25
11/01/90	082	REVISED PROTOCOL	CS# 087027-999 - AMENDMENT # 1 (OCTOBER 30, 1990)	25
11/14/90	083	INFORMATION AMENDMENT	Cover Letter, 1571 Form and Table of Contents	26
11/14/90	083	INFORMATION AMENDMENT	Clinical Bibliography	26
11/14/90	083	INFORMATION AMENDMENT	Pharmacology Bibliography	26
11/14/90	083	INFORMATION AMENDMENT	Toxicology Detailed Report	26
11/14/90	083	INFORMATION AMENDMENT	Report # 431i	26
11/14/90	083	INFORMATION AMENDMENT	Toxicology Published Report	26
11/14/90	083	INFORMATION AMENDMENT	Report # AX 0190	26
11/14/90	084	ADR REPORT	MFR# 08790026 - Foreign - P. Hurteloup, France - Cholestatic Hepatitis	26
11/16/90	085	ADR REPORT - FOREIGN	MFR# 08790027 - P. HURTELOUP - FRANCE - AGRANULOCYTOSIS	26
11/16/90	086	ADR REPORT - 3-DAY	MFR# 08790030 - CS# 087023-009 - BERNARD BIHARI - DEATH ON STUDY	26
11/19/90	087	ADD ASSOCIATE	CS# 087023-008 - DAVID SMITH - 2 ASSOCIATES	26
11/19/90	087	CHANGE ADDRESS & ADD ASSOC.	CS# 087027-007 - DAVID FEIGAL, JR. - 1 ASSOCIATE	26
11/19/90	087	NEW INVESTIGATOR	CS# 087023-025 - KENNETH WAYNE GREEN, JR. - 13 ASSOCIATES	26

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
10/04/90	077	ADR REPORT	MFR# 08790023 - CS# 087023-001 - S. NIGHTINGALE - DEATH ON STUDY	23
10/19/90	078	ADD ASSOCIATE	CS# 087023-024 - MELANIE THOMPSON - 1 ASSOCIATE	24
10/19/90	078	ADD ASSOCIATE	CS# 087027-007 - DAVID FEIGAL, JR. - 4 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087023-005 - SUSAN MILLER - 0 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087023-013 - DAVID COHN - 3 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087023-014 - JEANNE WALLACE - 2 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087023-028 - JEAN A. SMITH - 13 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087023-033 - ROBERT M. DUPLIS - 3 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087023-038 - ANTHONY LAMARCA - 0 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087027-001 - STANLEY C. DERENSINSKI - 4 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087027-016 - DONALD ROMIG - 6 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087027-019 - STEPHEN HAUPTMAN - 0 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087027-022 - ROBERTA LUSKIN - 9 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087027-026 - LINDA LOU CROCKER SMITH - 3 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087027-029 - JEFFREY GALPIN - 2 ASSOCIATES	24
10/19/90	078	NEW INVESTIGATOR	CS# 087027-033 - JOHN P. PHAIR - 7 ASSOCIATES	24
10/25/90	079	ADR REPORT (3 DAY REPORT)	MFR# 08790024 - CS# 087023-004 - D. KAUFMAN - SEVER ABDOMINAL PAIN (PHONE NOTIFICATION)	24
10/25/90	080	ADR REPORT	MFR# 08790025 - CS# 087023-023 - W. WEINBERG - CHOLESTATIC HEPATITIS, ENCEPHALOPATHY	24

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
09/12/90	072	INFORMATION AMENDMENT	AX 0123	23
09/12/90	072	INFORMATION AMENDMENT	AX 0185	23
09/12/90	072	INFORMATION AMENDMENT	AX 0186	23
09/12/90	072	INFORMATION AMENDMENT	AX 0188	23
09/12/90	072	INFORMATION AMENDMENT	PHARMACOLOGY BIBLIOGRAPHY	23
09/12/90	072	INFORMATION AMENDMENT	PHARMACOKINETICS DETAILED REPORT	23
09/12/90	072	INFORMATION AMENDMENT	617i	23
09/12/90	072	INFORMATION AMENDMENT	PHARMACOKINETICS BIBLIOGRAPHY	23
09/14/90	073	ADR REPORT	MFR# 08790020 - CS# 872309 - Bernard Bihari - Pancytopenia	23
09/14/90	073	ADR REPORT	MFR# 08790021 - Foreign - Australia (FICE) - Death with 30-Days of Ceasing Rifabutin	23
09/19/90	074	CHANGE ADDRESS & ADD ASSOC.	CS# 872321 - JOSEPH HAVLIK - 2 ASSOCIATES	23
09/19/90	074	NEW INVESTIGATOR	CS# 872710 - PETER JENSEN - 2 ASSOCIATES	23
09/19/90	074	NEW INVESTIGATOR	CS# 872720 - JOEL WEISMAN - 6 ASSOCIATES	23
09/19/90	074	NEW INVESTIGATOR	CS# 872724 - BARRY BERNSTEIN - 2 ASSOCIATES	23
09/19/90	074	NEW INVESTIGATOR	CS# 872728 - ALFRED F. BURNSIDE - 0 ASSOCIATES	23
09/24/90	075	ADR REPORT	MFR# 08790022 - CS# 087023-001 - DR. STEPHEN NIGHTINGALE - DEATH	23
09/28/90	076	ADR REPORT - FOREIGN	MFR# 08790013 - DR. SCHULER - BERLIN - CARDIOPULMONARY FAILURE, DEATH	23
09/28/90	076	ADR REPORT - FOREIGN	MFR# 08790016 - DR. SCHULER - BERLIN - ALOPECIA, CHOLESTASIS, PRURITUS/ALLERGIC REACTION, DEATH(SUICIDE)	23

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
07/18/90	067	NEW INVESTIGATOR	CS# 872331 - AMJAD NAJJAR - 0 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872703 - GEORGE PEREZ - 9 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872704 - TERRENCE CHEW - 3 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872708 - SANDY POMERANTZ - 2 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872709 - PAULA SPARTI - 9 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872718 - JOHN J. STERN - 4 ASSOCIATES	22
07/25/90	068	PROTOCOL AMENDMENT	REVISED PROTOCOL - CS#087025-999 - CASE REPORT FORMS	22
08/10/90	069	NEW INVESTIGATOR	CS# 872322 - ROBERT S. KLEIN - 3 ASSOCIATES	23
08/10/90	069	NEW INVESTIGATOR	CS# 872712 - MARCUS CONANT - 0 ASSOCIATES	23
08/10/90	069	NEW INVESTIGATOR	CS# 872713 - C. LYNN BESCH - 3 ASSOCIATES	23
08/10/90	069	NEW INVESTIGATOR	CS# 872717 - LAWRENCE CRANE - 0 ASSOCIATES	23
08/10/90	069	NEW INVESTIGATOR	CS# 872723 - LAWRENCE J. ERON - 3 ASSOCIATES	23
08/10/90	069	NEW INVESTIGATOR	CS# 872725 - STEVEN SCHEIBEL - 1 ASSOCIATE	23
08/20/90	070	ADR REPORT CORRECTION	CHANGING S# 059 MFR# FROM 08790009 TO 08790004 (CS# 087023-001)	23
08/24/90	071	ADR REPORT	MFR# 08790019 - CS# 872309 - S. CORT - DEATH ON STUDY	23
09/12/90	072	INFORMATION AMENDMENT	CLINICAL AND PRECLINICAL	23
09/12/90	072	INFORMATION AMENDMENT	CLINICAL BIBLIOGRAPHY	23
09/12/90	072	INFORMATION AMENDMENT	PHARMACOLOGY PUBLISHED REPORTS	23

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
06/19/90	063	INFORMATION AMENDMENT	REPORT# PK/BAR 3124-89-01	21
06/19/90	063	INFORMATION AMENDMENT	PHARMACOKINETICS BIBLIOGRAPHY	21
06/19/90	063	INFORMATION AMENDMENT	TOXICOLOGY DETAILED REPORT	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 430i	21
06/25/90	064	ADR REPORT - FOREIGN	MFR# 08790007 - Dr. B. Gazzard, London - Death	22
06/25/90	064	ADR REPORT - FOREIGN	MFR# 08790008 - Dr. B. Gazzard, London - Death	22
06/25/90	064	ADR REPORT - FOREIGN	MFR# 08790009 - Dr. B. Gazzard, London - Death	22
06/25/90	064	ADR REPORT - FOREIGN	MFR# 08790010 - Dr. B. Gazzard, London - Death	22
06/25/90	064	ADR REPORT - FOREIGN	MFR# 08790011 - Dr. B. Gazzard, London - Death	22
06/25/90	064	ADR REPORT - FOREIGN	MFR# 08790012 - Dr. Poggonsee, Berlin - Depression (Aggravated) / Psychosis	22
06/29/90	065	ADR REPORT - FOREIGN	MFR# 08790006 - DR. PIERRO DE TRUCHIS - HEMOLYTIC ANEMIA, FEVER, DEATH	22
07/17/90	066	GENERAL CORRESPONDENCE	Letter to Mark Caspi (AIDS Database) - Information Concerning CS# 087027 Protocol	22
07/18/90	067	ADD ASSOCIATE	CS# 872309 - BERNARD BIHARI - 2 ASSOCIATES	22
07/18/90	067	ADD ASSOCIATE	CS# 872319 - FRED GORDIN - 1 ASSOCIATE	22
07/18/90	067	NEW INVESTIGATOR	CS# 872315 - RICHARD E. CHAISSON - 0 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872323 - WINKLER G. WEINBERG - 12 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872324 - MELANIE THOMPSON - 12 ASSOCIATES	22
07/18/90	067	NEW INVESTIGATOR	CS# 872327 - PAUL CASNER - 0 ASSOCIATES	22

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
06/19/90	063	INFORMATION AMENDMENT	CLINICAL BIBLIOGRAPHY	21
06/19/90	063	INFORMATION AMENDMENT	PRECLINCAL INFORMATION	21
06/19/90	063	INFORMATION AMENDMENT	PHARMACOLOGY DETAILED REPORTS	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 087904-000 - FINAL REPORT	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 087901-000 - FINAL REPORT (REVISED)	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 087021-000 - FINAL REPORT (REVISED)	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 211i	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 212i	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 213i	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# 221i	21
06/19/90	063	INFORMATION AMENDMENT	PHARMACOLOGY PUBLISHED REPORTS	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# AX 0175	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# AX 0180	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# AX 0182	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# AX 0183	21
06/19/90	063	INFORMATION AMENDMENT	REPORT# AX 0184	21
06/19/90	063	INFORMATION AMENDMENT	PHARMACOLOGY BIBLIOGRAPHY	21
06/19/90	063	INFORMATION AMENDMENT	PHARMACOKINETICS DETAILED REPORT	21

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04/20/90	054	NEW INVESTIGATORS	CS# 872321 - JOSEPH HAVLIK - 2 ASSOCIATES	19
04/23/90	055	REVISED PROTOCOL	CS# 087023-999 - Description of Changes - Protocol - Case Report Forms	19
04/23/90	056	REVISED PROTOCOL	CS# 087039-000 - DESCRIPTION OF CHANGES - PROTOCOL	19
04/24/90	057	ADR REPORT - FOREIGN	MFR# 08790003 - DR. GILQUIN - FRANCE - DEATH ON STUDY	19
05/02/90	058	ADR REPORT / FOLLOW-UP	MFR# 08790001 - Foreign - Dr. Brodt - Germany - Cardiac Failure/Disseminated CMV Infection/Death	19
05/23/90	059	ADR REPORT	MFR# 08790004 - CS# 087023-001 - S. NIGHTINGALE,M.D. - PNEUMOCYSTIS, DEATH	19
05/25/90	060	NEW INVESTIGATOR	CS# 872306 - MICHAEL F. PARA - 10 ASSOCIATES	20
05/25/90	060	CHANGE OF ADDRESS	CS# 872303 - FREDERICK P. SIEGAL - 0 ASSOCIATES	20
05/25/90	060	CHANGE OF ADDRESS	CS# 872304 - DAVID KAUFMAN - 0 ASSOCIATES	20
05/25/90	060	CHANGE OF ADDRESS	CS# 872307 - PAUL CIMOCH - 0 ASSOCIATES	20
05/25/90	060	CHANGE OF ADDRESS	CS# 872308 - DAVID SMITH - 0 ASSOCIATES	20
05/25/90	060	CHANGE OF ADDRESS	CS# 872309 - BERNARD BIHARI - 0 ASSOCIATES	20
05/25/90	060	CHANGE OF ADDRESS	CS# 872321 - JOSEPH HAVLIK - 0 ASSOCIATES	20
05/25/90	060	CHANGE FACILITIES &	CS# 872319 - FRED GORDIN - 2 ASSOCIATES	20
05/25/90	060	ADD ASSOCIATES	CS# 872319 - FRED GORDIN - 2 ASSOCIATES	20
06/06/90	061	NEW PROTOCOL	CS# 087027-999 - PHASE III - PROTOCOL - CASE REPORT FORMS - LABELS	20
06/06/90	061	NEW INVESTIGATOR	CS# 872707 - DAVID FEIGAL, JR. - 1 ASSOCIATE	20
06/15/90	062	GENERAL CORRESPONDENCE	Response to Telephone Conversation on May 23, 1990 with Dr. Lisa Kammerman Concerning CS# 087023	20

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03/08/90	051	ANNUAL PROGRESS REPORT	DEATHS ON STUDY	19
03/08/90	051	ANNUAL PROGRESS REPORT	PATIENTS DISCONTINUED	19
03/08/90	051	ANNUAL PROGRESS REPORT	DRUG'S ACTIONS	19
03/08/90	051	ANNUAL PROGRESS REPORT	LIST OF PRECLINICAL STUDIES - Pharmacology, Pharmacokinetics, Toxicology	19
03/08/90	051	ANNUAL PROGRESS REPORT	MANUFACTURING / MICROBIOLOGICAL	19
03/08/90	051	ANNUAL PROGRESS REPORT	INVESTIGATIONAL PLAN	19
03/08/90	051	ANNUAL PROGRESS REPORT	INVESTIGATORS BROCHURE REVISIONS	19
03/08/90	051	ANNUAL PROGRESS REPORT	PHASE I PROTOCOL MODIFICATIONS (NOTHING TO REPORT)	19
03/08/90	051	ANNUAL PROGRESS REPORT	FOREIGN MARKETING DEVELOPMENTS (NOTHING TO REPORT)	19
03/08/90	051	ANNUAL PROGRESS REPORT	OUTSTANDING BUSINESS (NOTHING TO REPORT)	19
04/02/90	052	ADR REPORT	MFR# 08790001 - FOREIGN - DEATH, CARDIOVASCULAR FAILURE - DR. BRODT, GERMANY	19
04/05/90	053	ADR REPORT	MFR# 08790002 - CS# 087011-046 - D. PRINCE - PANCREATITIS	19
04/20/90	054	NEW INVESTIGATORS	CS# 872303 - FREDERICK P. SIEGAL - 0 ASSOCIATES	19
04/20/90	054	NEW INVESTIGATORS	CS# 872304 - DAVID KAUFMAN - 0 ASSOCIATES	19
04/20/90	054	NEW INVESTIGATORS	CS# 872308 - DAVID SMITH - 3 ASSOCIATES	19
04/20/90	054	NEW INVESTIGATORS	CS# 872309 - BERNARD BIHARI - 2 ASSOCIATES	19
04/20/90	054	NEW INVESTIGATORS	CS# 872312 - SADHANA SATHE - 2 ASSOCIATES	19
04/20/90	054	NEW INVESTIGATORS	CS# 872320 - EARL MATTHEW - 7 ASSOCIATES	19

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02/16/90	049	INFORMATION AMENDMENT	MANUFACTURING AND PACKAGING PROCEDURE	18
02/16/90	049	INFORMATION AMENDMENT	ACCEPTABLE LIMITS AND ANALYTICAL METHODS	18
02/16/90	049	INFORMATION AMENDMENT	INFORMATION SUFFICIENT TO SUPPORT STABILITY	18
02/16/90	049	INFORMATION AMENDMENT	UPDATED STABILITY DATA	18
02/16/90	049	INFORMATION AMENDMENT	RIFABUTIN CAPSULES	18
02/16/90	049	INFORMATION AMENDMENT	OVER-ENCAPSULATED RIFAMPIN CAPSULES	18
03/07/90	050	NEW INVESTIGATOR	CS# 872307 - PAUL CIMOCH - 2 ASSOCIATES	18
03/07/90	050	NEW INVESTIGATOR	CS# 872319 - FRED GORDIN - 4 ASSOCIATES	18
03/08/90	051	ANNUAL PROGRESS REPORT	REPORTING PERIOD (1/1/89 - 12/31/89)	19
03/08/90	051	ANNUAL PROGRESS REPORT	COVER LETTER, 1571 FORM, TABLE OF CONTENTS	19
03/08/90	051	ANNUAL PROGRESS REPORT	INTRODUCTION	19
03/08/90	051	ANNUAL PROGRESS REPORT	INDIVIDUAL STUDY INFORMATION	19
03/08/90	051	ANNUAL PROGRESS REPORT	CS# 087007	19
03/08/90	051	ANNUAL PROGRESS REPORT	CS# 087008	19
03/08/90	051	ANNUAL PROGRESS REPORT	CS# 087011	19
03/08/90	051	ANNUAL PROGRESS REPORT	CS# 087039	19
03/08/90	051	ANNUAL PROGRESS REPORT	FREQUENT/SERIOUS ADE's	19
03/08/90	051	ANNUAL PROGRESS REPORT	SAFETY REPORTS	19

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01/05/90	043	NEW PROTOCOL	Discription of Changes	17
01/05/90	043	NEW PROTOCOL	Protocol - CS# 087025-999 and Case Report Forms	17
01/05/90	043	NEW PROTOCOL	Protocol - CS# 087032-999 and Case Report Forms	17
01/09/90	044	REVISED PROTOCOL	CS# 087023-999 - DESCRIPTION OF CHANGES - PROTOCOL - CASE REPORT FORMS	18
01/19/90	045	NEW CLINICAL STUDY	Protocol CS# 087023-999 - Case Report Forms	18
01/19/90	045	NEW CLINICAL STUDY	CS# 087023-001 - Stephen Nightingale, M.D. (1 Associate)	18
01/19/90	045	NEW CLINICAL STUDY	Labels	18
01/22/90	046	GENERAL CORRESPONDENCE	Proposed Agenda for 2/8/90 Meeting with FDA - Participants	18
01/23/90		FDA LETTER	AIDS DRUG CLINICAL TRIAL DATA BANK - FILING REQUIREMENTS & FR NOTICES	18
02/14/90	047	GENERAL CORRESPONDENCE	Response to FDA Letter Dated 1/23/90 - Telephone Conversation of 1/26/90	18
02/16/90	048	NEW PROTOCOL	CS# 087040-000 - FOR ORAL DOSES OF RIFABUTIN - CASE RPT FORMS AND LABELS INCLUDED	18
02/16/90	048	NEW INVESTIGATOR	CS# 087040-000 - JAMES C. KISICKI - 2 ASSOCIATES	18
02/16/90	049	INFORMATION AMENDMENT	CLINICAL AND MANUFACTURING	18
02/16/90	049	INFORMATION AMENDMENT	CLINICAL - LITERATURE REPRINTS (5 PUBLISHED REPORTS INCLUDED)	18
02/16/90	049	INFORMATION AMENDMENT	CHEMISTRY, MFG AND CONTROLS	18
02/16/90	049	INFORMATION AMENDMENT	SECTION 7B - AMENDMENT	18
02/16/90	049	INFORMATION AMENDMENT	COMPONENTS	18
02/16/90	049	INFORMATION AMENDMENT	NAME/ADDRESS OF DRUG PRODUCT MANUFACTURER	18

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11/16/89	039	INFORMATION AMENDMENT	Report # 087021-000	17
11/16/89	039	INFORMATION AMENDMENT	Pharmacology Published Reports	17
11/16/89	039	INFORMATION AMENDMENT	Report # AX 0156	17
11/16/89	039	INFORMATION AMENDMENT	Report # AX 0158	17
11/16/89	039	INFORMATION AMENDMENT	Pharmacology Bibliography	17
11/16/89	039	INFORMATION AMENDMENT	Pharmacokinetics Detailed Report	17
11/16/89	039	INFORMATION AMENDMENT	Report # 087005	17
11/16/89	039	INFORMATION AMENDMENT	Pharmacokinetics Bibliography	17
11/27/89	040	CHANGE PRINCIPAL INV.	CS# 871142 - ARNOLD GORIN - O ASSOCIATES	17
11/27/89	041	NEW STUDY	Protocol CS# 087039-000 (Formerly 087019-000)	17
11/27/89	041	NEW STUDY	Sample Case Report Forms	17
11/27/89	041	NEW STUDY	CS# 873900 - Stephen Nightingale (2 associates)	17
11/27/89	041	NEW STUDY	Labeling	17
12/14/89		FDA LETTER	Project taken of Clinical Hold	17
12/22/89	042	CHANGE OF ADDRESS	CS# 087039-000 - STEPHEN D. NIGHTINGALE - O ASSOCIATES	17

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11/06/89	038	INFORMATION AMENDMENT	References 186 - 260	12
11/06/89	038	INFORMATION AMENDMENT	References 126 - 185	13
11/06/89	038	INFORMATION AMENDMENT	References 51 - 125	14
11/06/89	038	INFORMATION AMENDMENT	References 1 - 50	15
11/06/89	038	INFORMATION AMENDMENT	Interim Report Study # 087904	16
11/06/89	038	INFORMATION AMENDMENT	Final Report - H. Burger & B. Weiser - StonyBrook In-Vitro Studies	16
11/06/89	038	INFORMATION AMENDMENT	Review of Final report of Drs. Burger and Weiser	16
11/06/89	038	INFORMATION AMENDMENT	Perclinical Published Literature	16
11/06/89	038	INFORMATION AMENDMENT	Literature Assessment - M. Hurley & Associates 10-17-89	16
11/06/89	038	INFORMATION AMENDMENT	Tables	16
11/06/89	038	INFORMATION AMENDMENT	Bibliography - Addendix I	16
11/06/89	038	INFORMATION AMENDMENT	Tables - Addendix II	16
11/06/89	038	INFORMATION AMENDMENT	Adverse Experience Listing - Addendix III	16
11/16/89	039	INFORMATION AMENDMENT	Cover Letter, 1571 Form and Table of Contents	17
11/16/89	039	INFORMATION AMENDMENT	Interim Report	17
11/16/89	039	INFORMATION AMENDMENT	Clinical Bibliography	17
11/16/89	039	INFORMATION AMENDMENT	Pharmacology Detailed Reports	17
11/16/89	039	INFORMATION AMENDMENT	Report # 087901-000	17

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
05/22/89	N/A	DRAFT PROTOCOL	CS# 087025-999 - A Double-Blind Randomized Clinical Trial of a Rif Regimen in the Treatment of	N/A
05/22/89	N/A	DRAFT PROTOCOL	MAC Bacteria In Patients with AIDS	N/A
05/23/89	032	INFORMATION AMENDMENT	CHEMISTRY, MANUFACTURING & CONTROLS - UPDATED STABILITY DATA	8
05/24/89	031	ADD INVESTIGATOR	CS# 871179 - KECK HARTMAN - 2 ASSOCIATES	8
06/02/89		FDA LETTER	Placing Project on Clinical Hold	8
06/06/89	033	ADR REPORT (FOREIGN)	MFR# 08789008 - P. RUTGEERTS - ZIEKTEN, BELGIUM - NAUSEA, VOMITING, FEVER AND VERTIGO	8
06/06/89	033	ADR REPORT (FOREIGN)	MFR# 08789012 - M. REY - FERRAND, FRANCE - GRAND MAL SEIZURE	8
06/29/89	N/A	DRAFT PROTOCOL	CS# 087019-000 - Phase I Open Label Safety & Steady-State Pharmacokinetic Drug Interaction Trial	N/A
06/29/89	N/A	DRAFT PROTOCOL	of Rifabutin & Zidovudine in Patients with AIDS	N/A
08/01/89	034	REVISED PROTOCOL	CS# 087019-000 - REVISED 1572 FOR JUAN LERTORA - SUMMARY AND PROTOCOL	9
09/05/89	035	REVISED PROTOCOL	CS# 087019-000 - REVISED PROTOCOL AND SUMMARY	9
09/05/89	035	NEW PROTOCOL	CS# 087023-999 - NEW PROTOCOL AND SUMMARY	9
09/07/89	N/A	DRAFT PROTOCOL	CS# 087032-999 - A Double-Blind Randomized Rifabutin Dose Respone Trial for Treatment of	N/A
09/07/89	N/A	DRAFT PROTOCOL	MAC Bactermia in Patients with AIDS	N/A
09/22/89	036	ADR REPORT (CCD's IND)	MFR# 08789015 - A. O'BRIEN - HERMAN HOSPITAL - HOUSTON,TEXAS - PANCREATITIS	9
10/23/89	037	ADD INVESTIGATOR	CS# 871189 - BRUCE SHERLING - 0 ASSOCIATES	9
11/06/89	038	INFORMATION AMENDMENT	References 326 - 389 and 900	10
11/06/89	038	INFORMATION AMENDMENT	References 261 - 325	11

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04/12/89	027	INFO AMENDMENT	AX 0092	8
04/12/89	027	INFO AMENDMENT	AX 0001A	8
04/12/89	027	INFO AMENDMENT	AX 0118	8
04/12/89	027	INFO AMENDMENT	AX 0134	8
04/12/89	027	INFO AMENDMENT	Pharmacology Bibliography	8
04/12/89	027	INFO AMENDMENT	PHARMACOKINETICS	8
04/12/89	027	INFO AMENDMENT	Pharmacokinetics Bibliography	8
04/12/89	027	INFO AMENDMENT	TOXICOLOGY	8
04/12/89	027	INFO AMENDMENT	Toxicology Detailed Reports	8
04/12/89	027	INFO AMENDMENT	429i	8
04/19/89	028	ADR REPORT (FOREIGN)	MFR# 08789004 - MILANO, ITALY - P. GRIS - ACUTE RENAL FAILURE, DEATH	8
04/27/89	029	NEW PROTOCOL	CS# 087019-000 - PHASE I TRIAL - LABEL INCLUDED	8
04/27/89	029	ADD INVESTIGATOR	CS# 087019-000 - JUAN LERTORA - 3 ASSOCIATES	8
05/12/89	030	INFORMATION AMENDMENT	In-Vivo Effect of Rifabutin	8
05/12/89	030	INFORMATION AMENDMENT	Stonybrook Report - In-Vivo Studies:Anti-HIV-1 Activity of Rifabutin in Combination with AZT of ddC	8
05/12/89	030	INFORMATION AMENDMENT	Critique - Review of Final Report Regarding the Anti-HIV Activity of Rifabutin	8
05/12/89	030	INFORMATION AMENDMENT	Proposal for Testing the Effect of Rifabutin on HIV-1 Replaction in T Cells & Monocytes	8
05/22/89	N/A	DRAFT PROTOCOL	CS# 087023-999 - Rif Therapy for Prevention of (MAC) Bacteremia in Patients with AIDS	N/A

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03/15/89	025	PROGRESS RPT.	CS# 087011	8
03/15/89	025	PROGRESS RPT.	FREQUENT/SERIOUS ADE's	8
03/15/89	025	PROGRESS RPT.	SAFETY REPORTS	8
03/15/89	025	PROGRESS RPT.	DEATHS ON STUDY	8
03/15/89	025	PROGRESS RPT.	PATIENTS DISCONTINUED	8
03/15/89	025	PROGRESS RPT.	DRUG'S ACTIONS	8
03/15/89	025	PROGRESS RPT.	LIST OF PRECLINICAL STUDIES	8
03/15/89	025	PROGRESS RPT.	MANUFACTURING / MICROBIOLOGICAL	8
03/15/89	025	PROGRESS RPT.	INVESTIGATIONAL PLAN	8
03/15/89	025	PROGRESS RPT.	INVESTIGATORS BROCHURE REVISIONS (NOTHING TO REPORT)	8
03/15/89	025	PROGRESS RPT.	PHASE I PROTOCOL MODIFICATIONS (NOTHING TO REPORT)	8
03/15/89	025	PROGRESS RPT.	FOREIGN MARKETING DEVELOPMENTS (NOTHING TO REPORT)	8
03/15/89	025	PROGRESS RPT.	OUTSTANTING BUSINESS (NOTHING TO REPORT)	8
04/11/89	026	ADD INV	CS# 871109 - W. BROOKS EMORY - 3 ASSOCIATES	8
04/12/89	027	INFO AMENDMENT	CLINICAL	8
04/12/89	027	INFO AMENDMENT	Clinical Bibliography	8
04/12/89	027	INFO AMENDMENT	PHARMACOLOGY	8
04/12/89	027	INFO AMENDMENT	Pharmacology Detailed Reports	8

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02/17/89	022	INFO AMEND	AX 0089	7
02/17/89	022	INFO AMEND	Current Pharmacology Literature Citations	7
02/17/89	022	INFO AMEND	TOXICOLOGY	7
02/17/89	022	INFO AMEND	Toxicology Detailed Report (Unpublished)	7
02/17/89	022	INFO AMEND	428i	7
03/03/89	023	ADR REPORT	MFR# 08789002 - CS# 087008 - Walter Thayer - Grand Mal Seizure	7
03/06/89	N/A	FDA LETTER	4 COMMENTS ON RIFABUTIN PROTOCOL CS# 087011-999	7
03/09/89	024	ADD INV	CS# 871146 - DAVID S. PRINCE - 1 ASSOCIATE	8
03/09/89	024	ADD INV	CS# 871152 - DAVID Y. ROSENZWEIG - 5 ASSOCIATES	8
03/09/89	024	ADD INV	CS# 871182 - MICHAEL R. CRAIN - 1 ASSOCIATE	8
03/09/89	024	ADD INV	CS# 871183 - JOHNNY E. BATES - 0 ASSOCIATES	8
03/15/89	025	PROGRESS RPT.	REPORTING PERIOD (2/1/88 - 1/31/89)	8
03/15/89	025	PROGRESS RPT.	COVER LETTER, 1571 FORM, TABLE OF CONTENTS	8
03/15/89	025	PROGRESS RPT.	INTRODUCTION	8
03/15/89	025	PROGRESS RPT.	INDIVIDUAL STUDY INFORMATION	8
03/15/89	025	PROGRESS RPT.	CS# 087004	8
03/15/89	025	PROGRESS RPT.	CS# 087008	8
03/15/89	025	PROGRESS RPT.	CS# 087007	8

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DATE	SER#	TYPE OF SUBMISSION	LETTER / SUBJECT	VOL
01/06/89	018	ADD INV	CS# 871111 - E. DALE EVERETT - 5 ASSOCIATES	5
01/20/89	019	INFO AMEND	6 Responses to FDA Letter 10/6/88 - CS# 087011	5
01/20/89	020	INFO AMEND	4 RESPONSES TO FDA LETTER 10/11/88 (MFG AND CONTROLS)	5
02/07/89	021	ADD ASSOC	CS# 087008 - WALTER R. THAYER, JR. - 1 ASSOCIATE	6
02/07/89	021	ADD INV	CS# 871102 - DANIEL E. BANKS - 5 ASSOCIATES	6
02/07/89	021	ADD INV	CS# 871112 - JOSHUA FIERER - 4 ASSOCIATES	6
02/17/89	022	INFO AMEND	CLINICAL AND PRECLINICAL	7
02/17/89	022	INFO AMEND	Cover Letter	7
02/17/89	022	INFO AMEND	FDA Form 1571	7
02/17/89	022	INFO AMEND	CLINICAL	7
02/17/89	022	INFO AMEND	Clinical Study No. 087003	7
02/17/89	022	INFO AMEND	Final Report	7
02/17/89	022	INFO AMEND	Clinical Study Summary	7
02/17/89	022	INFO AMEND	Protocol and Amendments	7
02/17/89	022	INFO AMEND	Data Listings	7
02/17/89	022	INFO AMEND	Current Clinical Literature Citations	7
02/17/89	022	INFO AMEND	PHARMACOLOGY	7
02/17/89	022	INFO AMEND	Pharmacology Detailed Reports (Published)	7

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09/21/88	014	ADR RPT	MF# 08788005 - FOREIGN - VOMITING, NAUSEA AND EPIGASTRIC PAIN	4
09/21/88	014	ADR RPT	SUBJECT DIED FIVE DAYS AFTER RIFIBUTIN THERAPY DISCONTINUED	4
10/06/88	N/A	FDA LTR	6 COMMENTS - PROTOCOL SUBMITTED 5/11/88	4
10/11/88	N/A	FDA LTR	REQUEST ADDITIONAL INFORMATION HPLC METHOD	4
11/04/88	015	ADD INV	CS# 871131 - KESAVAN KUTTY - 1 ASSOCIATE	4
11/04/88	015	ADD INV	CS# 871169 - DAVID E. WILLIAMS - 5 ASSOCIATES	4
11/14/88	016	INFO AMEND	FINAL REPORT CS# 87005	5
11/14/88	016	INFO AMEND	APPENDICES	5
11/14/88	016	INFO AMEND	CLINICAL ABSTRACT AX0110	5
11/14/88	016	INFO AMEND	STABILITY DATA	5
11/14/88	016	INFO AMEND	PRECLINICAL PUBLISHED REPORT (Mycobacterium paratuberculosis ...)	5
12/02/88	017	ADD INV	CS# 871113 - RONALD B. GEORGE - 4 ASSOCIATES	5
12/02/88	017	ADD INV	CS# 871127 - RICHARD WAYNE KEARLEY - 3 ASSOCIATES	5
12/02/88	017	UPDATED CV	CS# 087008 - WALTER R. THAYER, JR. - 0 ASSOCIATES	5

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08/19/88	011	ADD INV	CS# 871123 - MICHAEL ISEMAN (1 ASSOC.)	4
08/19/88	011	ADD INV	CS# 871139 - JOHN MARTIN (1 ASSOC.)	4
08/19/88	011	ADD INV	CS# 871173 - ROY DONNERBERG (1 ASSOC.)	4
09/08/88	012	INFO AMEND	CLINICAL, PHARMACOLOGY, & TOXICOLOGY	4
09/08/88	012	INFO AMEND	TABLE OF CONTENTS	4
09/08/88	012	INFO AMEND	4. CLINICAL	4
09/08/88	012	INFO AMEND	48. CURRENT BIBLIOGRAPHY	4
09/08/88	012	INFO AMEND	8. PHARMACOLOGY/TOXICOLOGY	4
09/08/88	012	INFO AMEND	8A. PHARMACOLOGY DETAILED REPORTS	4
09/08/88	012	INFO AMEND	8B. TOXICOLOGY DETAILED REPORTS	4
09/08/88	012	INFO AMEND	8C. PHARMACOKINETICS/METABOLISM DETAILED REPORTS	4
09/08/88	012	INFO AMEND	8D.1. PHARMACOLOGY BIBLIOGRAPHY	4
09/08/88	012	INFO AMEND	8D.2. TOXICOLOGY BIBLIOGRAPHY	4
09/08/88	012	INFO AMEND	8D.3. PHARMACOKINETICS (ADME) BIBLIOGRAPHY	4
09/20/88	013	ADD INV	CS# 871101 - NORMAN ADAIR - 0 ASSOCIATES	4
09/20/88	013	ADD INV	CS# 871164 - MOATAZ TOBAN - 0 ASSOCIATES	4
09/21/88	014	ADR RPT	MF# 08788003 - FOREIGN - SONIA NATAL RIBEIRO - DEATH DURING STUDY	4
09/21/88	014	ADR RPT	MF# 08788004 - FOREIGN - SONIA NATAL RIBEIRO - DEATH DURING STUDY	4

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05/10/88	006	ANNUAL RPT	Phase I Protocol Modifications (Nothing to Report)	3
05/10/88	006	ANNUAL RPT	Foreign Marketing Developments (Nothing to Report)	3
05/10/88	006	ANNUAL RPT	Log of Outstanding Business (Nothing to Report)	3
05/11/88	007	NEW STUDY	Protocol # 087011	3
05/11/88	007	NEW STUDY	Sample Case Report Forms	3
05/11/88	007	NEW STUDY	CS# 871116 - Allen Goldman (+6 assoc.)	3
05/11/88	007	NEW STUDY	--LABELING-- (new labeling included)	3
05/17/88		FDA LETTER	REV'S FOR CLIN TRIAL FOR PULMONARY M. avium COMPLEX (MAC) DISEASE	3
05/31/88	008	INFO AMEND	Components will be Pruchased at Local Pharmacy at each Site	3
06/07/88		FDA LETTER	APPROVAL REVISED PROTOCOL CS# 087011-999 SUBMITTED 5/11/88	3
06/27/88	009	ADD INV	CS# 871117 - Donald Graham	3
06/27/88	009	ADD INV	CS# 871119 - J. Ocie Harris	3
06/27/88	009	ADD INV	CS# 871142 - David Nickeson	3
06/27/88	009	ADD INV	CS# 871151 - Charles Robertson	3
07/18/88	010	ADR REPORT	MFR# 08788002 - CS# 087008 - DEATH	4
08/19/88	011	ADD ASSO	CS# 087008 - WALTER R. THAYER (1 ASSOC.)	4
08/19/88	011	ADD INV	CS# 871107 - H. GUNNER DEERY	4
08/19/88	011	ADD INV	CS# 871121 - LINDA HEDEMARK	4

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05/10/88	006	ANNUAL RPT	Introduction	3
05/10/88	006	ANNUAL RPT	Brief Summary of Studies in Progress or Completed (4/1/87 - 1/31/88)	3
05/10/88	006	ANNUAL RPT	CS# 087004	3
05/10/88	006	ANNUAL RPT	CS# 087008	3
05/10/88	006	ANNUAL RPT	CS# 087007	3
05/10/88	006	ANNUAL RPT	Summary Information	3
05/10/88	006	ANNUAL RPT	Summary of Most Frequent and Most Serious Adverse Experiences -	3
05/10/88	006	ANNUAL RPT	Summary of Safety Reports Submitted 4/1/87 - 1/31/88	3
05/10/88	006	ANNUAL RPT	List of Patients Who Died "On-Study" 4/1/87 - 1/31/88	3
05/10/88	006	ANNUAL RPT	List of Patients Discontinued Toxicity/Adverse Reaction or Patient Refusal	3
05/10/88	006	ANNUAL RPT	Information Obtained Pertinent to an Understanding of the Drug's Actions	3
05/10/88	006	ANNUAL RPT	List of Preclinical Studies	3
05/10/88	006	ANNUAL RPT	Pharmacology	3
05/10/88	006	ANNUAL RPT	Pharmacokinetics/Metabolism	3
05/10/88	006	ANNUAL RPT	Significant Manufacturing or Microbiological Changes	3
05/10/88	006	ANNUAL RPT	Investigational Plan	3
05/10/88	006	ANNUAL RPT	Investigational Brochure Revisions (Nothing to Report)	3

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03/11/88	004	INFO AMEND	Detailed Reports - 609i, 610i, 802i, 803i, 811i	2
03/11/88	004	INFO AMEND	Detailed Reports (cont.) - 812i, 813i, 814i, 815i, 816i	2
03/11/88	004	INFO AMEND	Detailed Reports (cont.) - 817i, AX0047, AX0061	2
03/11/88	004	INFO AMEND	1.PHARMACOLOGY BIBLIOGRAPHY	2
03/11/88	004	INFO AMEND	2.PHARMACOKINETIC (ADME) BIBLIOGRAPHY	2
04/08/88	005	INFO AMEND	SECT.A - RESPONSE 1 -metobolic studies needed in animals	3
04/08/88	005	INFO AMEND	SECT.A - RESPONSE 2 -need toxicity data for dose levels above 450mg	3
04/08/88	005	INFO AMEND	SECT.A - RESPONSE 3 -interim results for mouse & rat CA studies	3
04/08/88	005	INFO AMEND	SECT.A - RESPONSE 4 -results of 1 yr. rat study needed	3
04/08/88	005	INFO AMEND	SECT.A - RESPONSE 5 -Heinz Bodiy formation	3
04/08/88	005	INFO AMEND	SECT.A - RESPONSE 6 -alternate-day administration	3
04/08/88	005	INFO AMEND	SECT.A - RESPONSE 7 -"Arneth's count"	3
04/08/88	005	INFO AMEND	SECT.B - MFG & CTRLS (a) use Swedish orange capsules	3
04/08/88	005	INFO AMEND	SECT.B - MFG & CTRLS (b) repackaging & labeling bottle & blister	3
04/08/88	005	INFO AMEND	SECT.B - MFG & CTRLS (c) new HPLC Assay method	3
04/08/88	005	INFO AMEND	SECT.B - MFG & CTRLS (d) composition,mfg,processing & pkging placebo	3
04/08/88	005	INFO AMEND	SECT.C - MFG & CTRLS - RIFAMPIN CAPSULES-overencapsulation with orange	3
05/10/88	006	ANNUAL RPT	Cover Letter, FD Form 1571, Table of Contents	3

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03/12/87		LTR FROM FDA	RESPONSE TO 7/3/86 SUBMISSION - ALSO REFERING TO 7/22/86 MEETING WITH FDA	1
03/19/87		LTR TO FDA	LETTER TO FDA IN REFERENCE TO CROHN'S DISEASE SUMITTED TO WRONG IND (3/13/87)	1
05/23/87		AMENDMENT	MFG/CONTROLS - CHANGE IN SPECIFICATION AND TEST METHODS - DRUG SUBSTANCE	1
07/02/87		CHG CLIN MON	CLINICAL MONITOR: MARGARET REAL,M.D. ASSOCIATE MON: BEVERLY WYNN	1
07/15/87		ADR REPORT	MFR# 08787001 /CS# FOREIGN /THROMBOCYTOPENIA-INTRACEREBRAL HEMORRHAGE	1
07/28/87		ADR REPORT	MFR# 08787003 /CS# FOREIGN /FEVER,MALAISE,MYALGIA,ARTHRALGIA	1
07/28/87		X-REF	CROSSREFERENCE ANNUAL PROG RPT FOR IND 27,934	1
08/05/87		ADD ASSOC INV	ADD TWO ASSOCIATE INVESTIGATORS FOR THAYER.,Jr.	1
09/25/87	001	X-REF	CROSSREF. MFR# 08787004 / CS# 8703 / MILD ARTHRALGIA	1
09/25/87	001	X-REF	CROSSREF. MFR# 08787005 / CS# 8703 / POLYARTICULAR ARTHRALGIA	1
09/25/87	001	X-REF	CROSSREF. MFR# 08787006 / CS# 8703 / POLYARTICULAR ARTHRALGIA	1
01/26/88	002	X-REF	CROSSREF. MFR# 08788001 / CS# 87003 / UVEITIS	1
01/27/88	003	NEW PROTOCOL	CS# 087011-999 & CASE REPORT FORMS	1
03/11/88	004	INFO AMEND	Cover Letter, FORM 1571, TABLE OF CONTENTS	2
03/11/88	004	INFO AMEND	PHARMACOLOGY/TOXICOLOGY	2
03/11/88	004	INFO AMEND	PHARMACOLOGY	2
03/11/88	004	INFO AMEND	Detailed Reports - 214i, 217i, 218i, 219i	2
03/11/88	004	INFO AMEND	PHARMACOKINETICS/METABOLISM	2

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01/08/87		ORIG SUBM	LETTER OF AUTHORIZATION	1
01/08/87		ORIG SUBM	LIST OF INVESTIGATORS FILED TO IND 27,934	1
01/08/87		ORIG SUBM	FORM 1571	1
01/08/87		ORIG SUBM	SECTION 1-9 ARE REFERENCED TO LOCATION IN IND 27,934 ON TABLE OF CONTENTS	1
01/08/87		ORIG SUBM	SECTION 10 - OUTLINE OF ANY PHASES OF PLANNED INVESTIGATIONS	1
01/08/87		ORIG SUBM	SECTION 10 - LIST OF INVESTIGATORS FILED TO IND 27,934	1
01/08/87		ORIG SUBM	SECTION 10 - PROTOCOL # 087004	1
01/08/87		ORIG SUBM	SECTION 10 - PROTOCOL # 087007	1
01/08/87		ORIG SUBM	SECTION 10 - DRAFT PROTOCOL / CDC	1
01/08/87		ORIG SUBM	SECTION 11 - FDA NOTIFICATION STATEMENT	1
01/08/87		ORIG SUBM	SECTION 12 - INVESTIGATORS NOTIFICATION STATEMENT	1
01/08/87		ORIG SUBM	SECTION 13 - NON-COMMERCIALIZATION	1
01/08/87		ORIG SUBM	SECTION 14 - 30-DAY DELAY OR WAIVER	1
01/08/87		ORIG SUBM	SECTION 15 - ENVIRONMENTAL IMPACT ANALYSIS	1
01/08/87		ORIG SUBM	SECTION 16 - CONFORMING AMENDMENT STATEMENT	1
01/14/87		NEW CLIN STDY	PROTOCOL # 087008 - RIFABUTIN & STEPTOMYCIN IN PATIENTS WITH SEVERE REFRACTORY DISEASE	1
01/14/87		NEW CLIN STDY	1572 FORM - WALTER THAYER	1
01/14/87		NEW CLIN STDY	LABELS	1

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10/12/92	200	REVISED PROTOCOL	CS# 087162-000 - Amendment # 2 (09/21/92) Summary of Revisions and Revised Protocol	167
10/13/92	201	CHANGE OF P.I.	CS# 087023-021 - Steven Gordon	167
10/15/92	202	INFORMATION AMENDMENT	Cross-Reference Final Reports CS# 087023 & 087027 into IND (Submitted to NDA 05/06/92)	167
10/19/92	203	AUTHORIZATION TO CROSS-REF	Letter Giving Pfizer Central Research Authorization to Cross-Reference Safety & Manuf. Data	167
10/19/92	204	ADR REPORT - FOREIGN	MFR# 08792069 - Foreign - B. Taillan, France - Pancreatitis, Hepatic Failure, Death	167
10/22/92	205	GENERAL CORRESPONDENCE	Letter Giving Division of AIDS (DAIDS) Authorization to Cross-Reference The Preclinical & MFG Data	167
11/09/92	206	ADR REPORT - FOREIGN	MFR# 08792075 - Foreign - A.M. Rogues, France - Cholestasis	167
11/09/92	207	REVISED PROTOCOL	CS# 087058-000 - Amendment# 1 (04/22/92) Summary of Revisions and Revised Protocol	167

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09/04/92	193	NEW PROTOCOL	CS# 087162-000 - An Assessment of the Bioavailability of Rif Suspension Dosage Form Relative to	166
09/04/92	193	NEW PROTOCOL	Capsule Following Single Oral Doses to Male Volunteers	166
09/04/92	193	NEW PROTOCOL	Lables	166
09/04/92	193	NEW PROTOCOL	1572 Form - James Kisicki, M.D. (2 Associates)	166
09/04/92	193	NEW PROTOCOL	Curricula Vitae - CS# 087162-000	166
09/10/92	194	INFORMATION AMENDMENT	Preliminary Summary of the Rifabutin/Fluconazole Interaction Study CS# 087058	166
09/14/92	195	UPDATED 1572 FORM	CS# 087023-046 - Paul Cimoch (Updated Address)	166
09/14/92	195	UPDATED 1572 FORM	CS# 087065-037 - Stanley Deresinski (Add 2 Associates/Delete 3 Associates - Add/Delete Labs)	166
09/14/92	195	NEW INVESTIGATOR	CS# 087065-041 - Barry Bernstein (5 Associates)	166
09/17/92	196	REVISED PROTOCOL	CS# 087162-000 - Amendment # 1 (09/09/92) Summary of Revisions and Revised Protocol	167
09/21/92	197	ADR REPORT	MFR# 08792055 - CS# 087027-504 - Emil Toma - Myositis	167
09/21/92	197	ADR REPORT	MFR# 08792056 - CS# 087027-503 - W. Cameron - Abdominal Pain	167
09/30/92	198	ADR REPORT - ADDENDUM	MFR# 08792055 - CS# 087027-504 - Attachment (Patients in Rif Studies with Myopathy)	167

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08/14/92	189	INFORMATION AMENDMENT	Appendix II - Supportive Bioanalytical Documentation	165
08/14/92	190	NEW INVESTIGATOR	CS# 087065-027 - WINKLER WEINBERG - ADD 19 ASSOC. - DRUG SHIPMENT ADDRESS	166
08/14/92	190	CHANGE OF P.I.	CS# 087023-021 - THOMAS SZCZEPONIK - DELETE 1 ASSOC. - DRUG SHIPMENT ADDRESS	166
08/14/92	190	UPDATE 1572	CS# 087023-001 - STEPHEN NIGHTINGALE - ADD 1 LAB	166
08/14/92	190	UPDATE 1572	CS# 087023-004 - DAVID KAUFMAN - ADDRESS UPDATE	166
08/14/92	190	UPDATE 1572	CS# 087023-006 - MICHAEL F. PARA - ADD 1 LAB	166
08/14/92	190	UPDATE 1572	CS# 087023-009 - BERNARD BIHARI - ADD 2 ASSOC. - DELETE 2 ASSOC. - ADD 1 FACILITY	166
08/14/92	190	UPDATE 1572	CS# 087027-036 - STEVEN W. HALL - ADDRESS UPDATE	166
08/14/92	190	UPDATE 1572	CS# 087027-037 - MARSHALL KUBOTA - ADD 1 IRB	166
08/14/92	190	UPDATE 1572	CS# 087065-021 - PETER JENSEN - ADD 1 LAB	166
08/14/92	190	UPDATE 1572	CS# 087065-030 - PAUL CIMOCH - ADD 1 ASSOCIATE - ADD 1 FACILITY	166
08/14/92	190	UPDATE 1572	CS# 087065-035 - DAVID DRENNAN - ADD 1 LAB	166
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07/14/92	186	NEW INVESTIGATOR	CS# 087065-042 - GEORGE PEREZ - P.I. ADDRESS - NO ASSOCIATES	162
07/14/92	186	UPDATE 1572	CS# 087023-013 - DAVID COHN - DELETE 2 ASSOC. - DELETE 1 FACILITY, 1 IRB	162
07/14/92	186	UPDATE 1572	CS# 087023-027 - PAUL R. CASNER - ADD 1 ASSOC. - ADD 1 LAB	162
07/14/92	186	UPDATE 1572	CS# 087027-004 - TERRENCE CHEW - ADD 1 ASSOC.	162
07/14/92	186	UPDATE 1572	CS# 087027-512 - IGNATIUS FONG - P.I. ADDRESS UPDATE	162
07/14/92	186	UPDATE 1572	CS# 087058-000 - JAMES P. LAVELLE - ADD 1 ASSOC. - P.I. ADDRESS UPDATE	162
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08/06/92	188	ADR REPORT	MFR# 08792047 - Foreign - France - Anemia, Thrombocytopenia, leucopenia, Gram-negative sepsis, death	163

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05/22/92	180	ADR REPORT	MFR# 08791092 - Foreign Compassionate Use - Cholestatic Hepatitis	161
06/02/92	181	ADR REPORT	MFR# 08792033 - Foreign - Marseille, France - Thrombocytopenia	161
06/24/92	182	ADR REPORT-FOLLOW UP	MFR# 08792026 - CS# 087027-023 - Lawrence J. Eron - Thrombotic Thrombocytopenic Purpura	161
06/24/92	182	ADR REPORT	MFR# 08792037 - CS# 087027-025 - Steve Scheibel - Disseminated Intravascular Coagulation	161
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04/14/92	175	NEW INVESTIGATOR	CS# 087065-037 - Stanley Deresinski - 8 Assoc.	161
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04/14/92	175	UPDATE 1572	CS# 087027-017 - Lawrence Crane - Drug Shipment Address	161
04/14/92	175	UPDATE 1572	CS# 087027-038 - Carol Brosgart - Add 1 Assoc. - Additional Lab.	161
04/14/92	175	UPDATE 1572	CS# 087027-506 (Canada) - Anita Rachlis - P.I. Address	161
04/14/92	175	UPDATE 1572	CS# 087065-030 - Paul Cimoch - Delete 1 Assoc.	161
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05/07/92	177	ADR REPORT	MFR# 08792024 - CS# 087023-001 - Stephen Nightingale - Deep Vein Thrombosis	161
05/07/92	177	ADR REPORT	MFR# 08792025 - CS# 087023-008 - David L. Smith - Pulmonary Embolus	161
05/07/92	177	ADR REPORT-FOLLOW UP	MFR# 08792023 - CS# 087027-019 - Stephen P. Hauptman - Gastrointestinal Hemorrhage, Duodenal Ulcers	161
05/07/92	177	ADR REPORT-FOLLOW UP	MFR# 08792010 - CS# 087027-501 - Stephen Shafran - Deep Vein Thrombosis and Pulmonary Embolus	161
05/13/92	178	ADR REPORT	MFR# 08792027 - CS# 087027-007 - David Feigal - Thrombophlebitis	161
05/13/92	178	ADR REPORT	MFR# 08792028 - CS# 087027-025 - Steven Scheibel - Grand Mal Seizures	161
05/13/92	178	ADR REPORT	MFR# 08792026 - CS# 087027-023 - Lawrence J. Eron - Thrombotic Thrombocytopenic Purpura	161
05/21/92	179	ADR REPORT - CORRECTION	MFR# 08792027 - CS# 087027-007 - D. Feigal - Thrombophlebitis (Initial Submitted 05/13/92 - Serial# 178)	161
05/22/92	180	ADR REPORT	MFR# 08792029 - Richard Chaisson - Hepatitis	161

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03/04/92	171	UPDATE 1572	CS# 087027-507 (CANADA) - FIONA SMAILL - DELETE 2 ASSOC.	160
03/04/92	171	UPDATE 1572	CS# 087065-006 - FRED GORDIN - DRUG SHIPMENT ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087065-008 - NANCY KLIMAS - DRUG SHIPMENT ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087065-021 - PETER JENSEN - DRUG SHIPMENT ADDRESS	160
03/31/92	172	NEW CLINICAL STUDY	CS# 087058-000 Phase I Steady-State,Pharmacokintic & Safety Drug Interaction of	161
03/31/92	172	NEW CLINICAL STUDY	Rifabutin & Fluconazole in HIV (+) Patients	161
03/31/92	172	NEW CLINICAL STUDY	1572 Form - James Lavelle	161
03/31/92	172	NEW CLINICAL STUDY	Curricula Vitae - James Lavelle (2 Associates- Mary Young, Carol Trapnell)	161
03/31/92	172	NEW CLINICAL STUDY	Labels	161
03/31/92	173	ADR REPORT - FOLLOW-UP	MFR# 08791091 - Foreign - Germany - Dr. Vocks-Hauck - Aplastic Anemia/Fatal Gastrointestinal Bleeding	161
03/31/92	173	ADR REPORT	MFR# 08792010 - CS# 087027-501 - Stephen Shafran - Deep Vein Thrombosis/Pulmonary Embolus	161
04/10/92	174	ADR REPORT	MFR# 08792011 - CS# 087023-019 - Fred Gordin - Deep Vein Thrombosis	161
04/10/92	174	ADR REPORT	MFR# 08792012 - CS# 087023-009 - Bernard Bihari - Deep Vein Thrombosis and Pulmonary Embolus	161
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04/14/92	175	NEW INVESTIGATOR	CS# 087065-005 - Aaron Glatt - 3 Assoc. - Drug Shipment Address	161
04/14/92	175	NEW INVESTIGATOR	CS# 087065-015 - William Reiter - 1 Assoc.	161
04/14/92	175	NEW INVESTIGATOR	CS# 087065-016 - Anthony LaMarca	161
04/14/92	175	NEW INVESTIGATOR	CS# 087065-032 - Michael Nakata - 3 Assoc.	161

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03/04/92	171	CHANGE OF P.I.	CS# 087027-007 - DANIEL PEARCE	160
03/04/92	171	CHANGE OF P.I.	CS# 087065-019 - DANIEL PEARCE	160
03/04/92	171	UPDATE 1572	CS# 087023-001 - STEPHEN D. NIGHTINGALE - P.I. ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087023-021 - JOSEPH HAVLIK - ADD 1/DELETE 1 ASSOC.	160
03/04/92	171	UPDATE 1572	CS# 087023-023 - WINKLER WEINBERG - 2 UPDATED CV's	160
03/04/92	171	UPDATE 1572	CS# 087023-037 - JOHN CAREY - DRUG SHIPMENT ADDRESS - UPDATED CV	160
03/04/92	171	UPDATE 1572	CS# 087027-004 - TERRENCE CHEW - DELETE 1 ASSOC. - DRUG SHIPMENT ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087027-009 - PAULA SPARTI - ADD 4/DELETE 7 FACILITIES	160
03/04/92	171	UPDATE 1572	CS# 087027-016 - DONALD ROMIG - DRUG SHIPMENT ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087027-018 - JOHN J. STERN - DELETE 1 ASSOC.	160
03/04/92	171	UPDATE 1572	CS# 087027-019 - STEPHEN HAUPTMAN - DRUG SHIPMENT ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087027-022 - ROBERTA LUSKIN - DRUG SHIPMENT ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087027-025 -STEVEN SCHEIBEL - ADD 1/DELETE 1 IRB	160
03/04/92	171	UPDATE 1572	CS# 087027-026 - LINDA LOU SMITH - P.I. ADDRESS - DRUG SHIPMENT ADDRESS - FACILITY ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087027-031 - FRANK RHAME - DRUG SHIPMENT ADDRESS	160
03/04/92	171	UPDATE 1572	CS# 087027-033 - JOHN P. PHAIR - ADD 1 ASSOC. - ADD FACILITY	160
03/04/92	171	UPDATE 1572	CS# 087027-039 - ROSS HEWITT - DRUG SHIPMENT ADDRESS	160

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01/27/92	166	ADR REPORT	MFR# 08790032 - CS# 087027-026 - L. Smith - Pancytopenia	159
01/27/92	166	ADR REPORT	MFR# 08791003 - CS# 087023-001 - S. Nightingale - Fatal Hepatitis, Hepatic Coma, Pancreatitis	159
01/27/92	166	ADR REPORT	MFR# 08791005 - CS# 087027-008 - S. Pomerantz - Grade IV Neutropenia, Liver Dysfunction	159
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01/27/92	166	ADR REPORT	MFR# 08791019 - CS# 087027-018 - J. Stern - Seizure Preceded by Syncope	159
01/27/92	166	ADR REPORT	MFR# 08791046 - CS# 087027-010 - P. Jensen - Hepatitis	159
01/27/92	166	ADR REPORT	MFR# 08791047 - CS# 087027-009 - P. Sparti - Neutropenia, Thrombocytopenia, Anemia	159
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02/04/92	168	ADR REPORT	MFR# 08792004 - CS# 087027-007 - San Diego Co. Research Group - Severe Peripheral Neuropathy	159
02/13/92	169	ADR REPORT-FOLLOW UP	Correction - MFR# 08790031 - CS# 087027-004 - T. Chew - Grade IV Neutropenia	159
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01/23/92	163	ADR REPORT	MFR# 08790030 - CS# 087023-009 - B. Bihari - Death on Study	159
01/23/92	163	ADR REPORT	MFR# 08790035 - CS# 087023-004 - D. Kaufman - Right Visual Field Loss	159
01/23/92	163	ADR REPORT	MFR# 08791013 - CS# 087023-023 - W. Weinberg - Thrombotic Thrombocytopenic Purpura	159
01/23/92	163	ADR REPORT	MFR# 08791023 - CS# 087023-007 - W. Reiter - Grand Mal Seizures	159
01/23/92	163	ADR REPORT	MFR# 08791035 - CS# 087023-008 - M. Gupta - Mental Status Changes, Fever, Myoclonic jerks, Nausea, Vomit	159
01/23/92	163	ADR REPORT	MFR# 08791050 - CS# 087023-001 - J. Beall - Hepatitis, Altered Mental Status, Seizure Disorder	159
01/23/92	163	ADR REPORT	MFR# 08791051 - CS# 087023-028 - J. Smith - Anemia, Neutropenia	159
01/23/92	163	ADR REPORT	MFR# 08791055 - CS# 087023-019 - F. Gordin - Anemia	159
01/23/92	164	ADR REPORT	MFR# 08790020 - CS# 087023-009 - B. Bihari - Pancytopenia	159
01/23/92	164	ADR REPORT	MFR# 08790022 - CS# 087023-001 - S. Nightingale - Death	159
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01/13/92	160	ADR REPORT	Pancreatitis/Diabetic Ketoacidosis/Colitis due to C. difficile	159
01/14/92	161	ADR REPORT	CS# 087023-023,-003/MFR#'S 08791029, 08791030 /Seizure, temporal lobe epilepsy (tenative diagnosis)	159
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08/20/91	139	ADR REPORT	MFR# 08791055 - CS# 087023-019 - Fred Gordin - Anemia	85
08/21/91	138	UPDATE 1572	CS# 087023-003 - FREDRICK P. SIEGEL, M.D. - 3 ADDITIONAL LABS	85

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07/09/91	129	UPDATE 1572	CS# 087027-037 - MARSHALL KUBOTA - ADD 1 ASSOCIATE - DELETE FACILITY	61
07/09/91	129	UPDATE 1572	CS# 087065-020 - SANDY POMERANTZ - ADD 1 ASSOCIATE - DRUG SHIPMENT ADDRESS/PATIENT# 20001 - ADD IRB	61
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07/18/91	132	ADR REPORT - FOREIGN	MFR# 08791038 - B. LEBAS-ROUEN - FICE, FRANCE - THROMBOCYTOPENIA, LIVER ENZYMES INCREASED IN BLOOD...	61
07/18/91	132	ADR REPORT - FOREIGN	MFR# 08791041 - V. MONDAIN - FICE, FRANCE - ANEMIA, THROMBOCYTOPENIA, LEUCOPENIA & HEPATIC ENZYME...	61
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07/09/91	129	UPDATE 1572	CS# 087023-026 - SCOTT LEA - ADD IRB - DELETE IRB	61
07/09/91	129	UPDATE 1572	CS# 087023-027 - PAUL CASNER - ADD 1 ASSOCIATE - ADDITIONAL LABS - DELETE LAB	61
07/09/91	129	UPDATE 1572	CS# 087023-029 - LAUREN HOBRATSCH - ADD 1 ASSOCIATE - ADITIONAL LABS - DELETE LAB	61
07/09/91	129	UPDATE 1572	CS# 087023-031 - AMJAD NAJJAR - NEW ZIP CODE	61
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07/09/91	129	UPDATE 1572	CS# 087027-007 - DAVID FEIGAL - ADD 2 ASSOCIATES	61
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07/09/91	129	NEW INVESTIGATOR	CS# 087065-007 - NELSON ZIDE - 1 ASSOCIATE	61
07/09/91	129	NEW INVESTIGATOR	CS# 087065-008 - NANCY KLIMAS - 2 ASSOCIATES	61

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06/14/91	125	ADR REPORT	MFR# 08791035 - CS# 087023-008 - M. Gupta - Mental Status Changes, fever, myoclonic jerks, nausea &	55
06/14/91	125	ADR REPORT	vomiting, & polydipsia	55

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05/08/91	118	NEW INVESTIGATOR	CS# 087065-036 - BISHER AKIL - 13 ASSOCIATES	43
05/10/91	119	REVISED PROTOCOL	CS# 087027-999 - AMENDMENT #3 (APRIL 29, 1991) ddC SITES ONLY - 004 & 009	44
05/16/91	121	ADR REPORT	MFR# 08791029 - CS# 087023-023 - W. Weinberg - Seizure/Temporal Lobe Epilepsy (Tentative Diagnosis)	44
05/20/91	120	ADR REPORT	MFR# 08791030 - CS# 087023-003 - F. Siegal - Pancreatitis	44
05/22/91	122	INFORMATION AMENDMENT	CLINICAL - FINAL REPORT - CS# 087033-999 - CDC	44-48
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05/08/91	118	ADD ASSOCIATE	CS# 087023-009 - BERNARD BIHARI - ADD 1 ASSOCIATE	43
05/08/91	118	ADD &/OR DELETE ASSOCIATE	CS# 087023-023 - WINKLER G. WEINBERG - ADD 8 & DELETE 3 ASSOCIATES	43
05/08/91	118	ADD ASSOCIATE	CS# 087023-031 - AMIAD NAJJAR - ADD 2 ASSOCIATES	43
05/08/91	118	ADD ASSOCIATE	CS# 087027-007 - DAVID FEIGAL - ADD 4 ASSOCIATES	43
05/08/91	118	UPDATE 1572	CS# 087027-008 - SANDY POMERANTZ - NEW ZIP CODE	43
05/08/91	118	DELETE ASSOCIATE	CS# 087027-008 - SANDY POMERANTZ - DELETE 1 ASSOCIATE	43
05/08/91	118	UPDATE 1572	CS# 087027-013 - C. LYNN BESCH - ADDITIONAL FACILITY	43
05/08/91	118	UPDATE 1572	CS# 087027-020 - JOEL WEISMAN - NEW ADDRESS & ADDITIONAL FACILITY	43
05/08/91	118	NEW INVESTIGATOR	CS# 087027-037 - MARSHALL KUBOTA - 0 ASSOCIATES	43
05/08/91	118	NEW INVESTIGATOR	CS# 087027-039 - ROSS G. HEWITT - 0 ASSOCIATES	43
05/08/91	118	NEW INVESTIGATOR - CANADA	CS# 087027-506 - ANITA RACHLIS - 1 ASSOCIATE	43
05/08/91	118	NEW INVESTIGATOR - CANADA	CS# 087027-512 - IGNATIOUS FONG - 0 ASSOCIATES	43
05/08/91	118	NEW INVESTIGATOR - CANADA	CS# 087027-513 - ANDREW SIMOR - 0 ASSOCIATES	43
05/08/91	118	NEW INVESTIGATOR	CS# 087065-006 - FRED GORDIN - 2 ASSOCIATES	43
05/08/91	118	NEW INVESTIGATOR	CS# 087065-012 - LAWRENCE J. ERON - 3 ASSOCIATES	43
05/08/91	118	NEW INVESTIGATOR	CS# 087065-019 - DAVID FEIGAL - 0 ASSOCIATES	43
05/08/91	118	NEW INVESTIGATOR	CS# 087065-020 - SANDY POMERANTZ - 1 ASSOCIATE	43
05/08/91	118	NEW INVESTIGATOR	CS# 087065-021 - PETER JENSEN - 2 ASSOCIATES	43

DATE/TYPE	CONTACT	SUBJECT
7/2/92 telecon	Schmuff	CMC issues
7/2/92 fax	Schmuff	Addresses for samples
6/25/92 - 7/16/92 telecons	Edison	Update of Schoenfelder/Wertz/Bryan telecons
7/6/92 telecon	Gosey/Goldberger/Isom	Microbiological issues
7/8/92 fax	Isom	Treatment IND - corrected copy of journal ad
7/8/92 telecon	Edison/Isom	Analyses
7/9/92 fax	Edison	List of analyses planned (Schoenfelder)
7/9/92 telecon	Isom	Treatment IND ad
7/14/92 letter	Layloff	Samples
7/14/92 Amend 40	Feigal	Response to Part 2, Point 6, 4/1/92 fax
7/16/92 - 7/25/92 telecons	Edison	Update of Schoenfelder/Wertz/Bryan telecons
7/17/92 letter	NIAID to Feigal	Serial No. 003 to NIAID IND
7/20/92 telecon	Schmuff	CMC section to Joe Graham
7/23/92 fax	Isom	Draft of task list
7/23/92 letter	Feigal	IA - Revised Investigator's Brochure
7/23/92 letter	Feigal	Treatment IND 008 - revised investigators brochure
7/24/92 letter	Edison from Bryan	Diskettes
7/24/92 fax	Edison	Treatment IND trip synopsis
7/27/92 letter	Edison from Bryan	Diskettes
7/27/92 fax	Isom	Search Alliance article, pregnancy statement
7/27/92 letter	Lillie	Investigator IND canceled - Joseph Steeger
7/28/92 letter	Feigal	Treatment IND 009 - investigators list
7/29/92 letter	Knippen to Versteegh	Treatment IND advertisement
7/31/92 fax	Edison to Bryan	Patient listings
8/3/92 fax	Edison	Tabulation of activities - John Schoenfelder
8/4/92 letter	Graham	Desk copy of Sections 3&4
8/5/92 telecon	Isom/Goldberger/Lepay	MetPath audit

DATE/TYPE	CONTACT	SUBJECT
8/5/92 Amend 41	Feigal	Responses to Mallikaarjun's fax
8/6/92 fax	Isom	BACTEC results
8/10/92 fax	Isom	Treatment IND draft letter to investigators
8/10/92 fax	Isom	Procedure protocol to Dr. Gosey
8/11/92 fax	Isom	Suggested revisions for protocol/doctor letter
8/12/92 fax	Edison	Quality of life article
8/13/92 fax	Edison	Tabulation changes from J. Schoenfelder
8/14/92 T-IND	Feigal	Treatment IND protocol amendment
8/13/92 Amend 42	Feigal	087056 final report (ddI interaction)
8/14/92 IND	Feigal	087056 final report to IND
8/14/92 fax	Isom	T-IND revised letter to physicians
8/17/92 Amend 43	Feigal	Response to MetPath 483
8/18/92 Amend 44	Feigal	Diskette for R. Edison
8/18/92 Amend 45	Feigal	Response to BACTEC results
8/18/92 telecon	Edison/Schoenfelder	Status of SAS data sets
8/18/92 letter	Feigal	DATRI 001 - Serial No. 004
8/19/92 Amend 46	Feigal	Diskette for Dr. Mallikaarjun
8/19/92 Amend 47	Feigal	Diskettes for R. Edison
8/20/92 Amend 48	Feigal	Diskette for R. Edison
8/21/92 Amend 49	Feigal	Diskette for R. Edison
8/21/92 telecon	Sylvester West	Impurities
8/21/92 letter	Feigal	Protocol amendment/new protocol (methadone interaction)
8/25/92 letter	Sylvester West	Response to 8/21 telecon
8/26/92 fax	Isom	Battelle report
8/26/92 telecon	Isom/Goldberger/ Edison/Lepay	Conclusions of FDA meeting with OSI
8/27/92 IA	Feigal	CMC IA/oral suspension
8/27/92 Amend 50	Feigal	Diskette for Dr. Mallikaarjun
8/27/92 letter	Feigal	DATRI 001 - Serial No. 005

DATE/TYPE	CONTACT	SUBJECT
7/16/92 - 8/31/92 telecons	Edison	Update of Wertz/Bryan/Schoenfelder telecons
8/31/92 telecon	West	MJW telecon
9/2/92 Amend 51	Feigal	Copy of documentation sent to Dr. Graham
9/2/92 letter	Pelsor	Copy of NONMEM files sent to Dr. Mallikaarjun
9/2/92 fax	Isom	Effects of rifabutin on *M. avium* in blood during transport
9/2/92 T-IND	Feigal	Investigators
9/3/92 letter	Edison	Desk copy of PI, responses to 1/4/6/9
9/3/92 letter	Isom	Desk copies of suspension dosage form protocol
9/4/92 fax	Pelsor	Information requested from P.K.
9/4/92 Ser. 193	Feigal	Suspension dosage form protocol
9/9/92 letter	Edison	Desk copy of responses to committee requests 3,5,8,10
9/9/92 Amend 52	Feigal	Rifabutin/fluconazole interaction study summary
9/10/92 Ser. 194	Feigal	Rif/Flu interaction study to IND
9/10/92 fax	Edison	Rif/Flu study summary
9/10/92 letter	Feigal	90 additional days - Dec. 12, 1992
9/10/92 letter	Isom	Desk copies of proposed backgrounder
9/11/92 telecon	Pelsor	P.K. Narang
9/11/92 fax	Pelsor	(PK) frequency distribution and histogram
9/11/92 telecon	Isom	Harris bioequivalence study
9/11/92 letter	Edison	J. Schoenfelder disk/letter
9/11/92 fax	Edison	Revised response - 2
9/14/92 fax	Edison	Revised-revised response - 2
9/14/92 telecon	Isom/Pelsor/Edison	PK issues/answers to committee questions
9/15/92 fax	Isom	Draft agenda
9/15/92 letter	Isom	Backgrounder
9/15/92 Amend 53	Feigal	Backgrounder
9/16/92 fax	Isom	Viability of *M. avium* in rifabutin-containing blood
9/16/92 fax	Isom	FDA draft agenda for 9/24 meeting

DATE/TYPE	CONTACT	SUBJECT
9/17/92 Amend 54	Feigal	Package Insert
9/17/92 Ser. 196	Feigal	087162 protocol amendment #1
9/21/92 Ser. 197	Feigal	Safety Report
9/21/92 letter	Edison	Desk copy - 5 ddI/rifabutin AEs
9/21/92 letter	Pelsor	PK - figure requested
9/21/92 letter	Isom	Table 1/diskette with ZDV levels
9/24/92 overheads	Edison	Robins' presentation to Advisory Committee
9/25/92 telecon	Schmuff	CMC issues, methods validation, environmental assessment
9/30/92 Ser. 198	Feigal	Safety Report
10/1/92 letter	Vincent	M. Williamson - environmental assessment
10/1/92 Amend 55	Feigal	Tabulations/diskettes requested by R. Edison
10/1/92 Amend 56	Feigal	RLW resignation
10/1/92 Ser. 199	Feigal	RLW resignation
10/6/92 fax	Isom	Draft package insert
8/31/92 - 10/6/92 telecons	Edison	Updates of Bryan/Wertz/Schoenfelder/Siegal contacts with Robin Edison
10/8/92 fax	Isom	LRV's correct phone number
10/12/92 Ser. 200	Feigal	Protocol Amendment 2 (087162)
10/12/92 Amend 57	Feigal	Letter of authorization - computer
10/13/92 fax	Isom	Letter of authorization
10/15/92 fax	Isom	Pg. 10 of draft PI
10/15/92 Amend 58	Feigal	Copy of documentation sent to Dr. Graham
10/15/92 Amend 59	Feigal	Updated analyses/integrated safety information (R. Edison)
10/19/92 Release	FDA Press Office	Press office release - AIDS Update
10/19/92 #203	Feigal	Pfizer Authorization to Cross-Reference IND
10/21/92 fax	Isom	Copies of art boards (revised labels for containers)
10/21/92 T#012	Feigal	Investigators - TIND #012
10/22/92 #205	Feigal	DAIDS Authorization to Cross-Reference IND
10/23/92 fax	Isom	FDA revisions for package insert

DATE/TYPE	CONTACT	SUBJECT
10/27/92 Amend 60	Feigal	Final printed labels (bottles, blister pack, carton)
10/27/92 Amend 61	Feigal	Response to Pelsor
10/28/92 Amend 62	Feigal	Response to R. Edison (adverse events)
10/16-28/92 telecons	Schmuff	Chemistry
10/16-30/92 telecons	Isom	Package Insert/labels
10/29/92 letter	Edison	Desk copy of safety information
10/30/92 fax	Isom	Chemistry - PI
11/2/92 fax	Isom	Clinical - PI
11/4/92 fax	Isom	Microbiology - PI
11/4/92 letter	Gosey	Article requested
11/4/92 Amend 63	Feigal	Response to Edison - pediatric
11/4/92 fax	Isom	Response to Gosey - kinetics and activity of metabolites
11/9/92 #207	Feigal	Protocol Amendment 087058
11/9/92 Amend 64	Feigal	Response to Edison (Schoenfelder)
11/9/92 #006	Hamrell to Feigal	NIAID IND 39,069
11/11/92 Amend 65	Feigal	Revised package insert
11/16/92 telecon	Schmuff	ALC/MJW - questions on active drug substance
11/16/92 Amend 66	Feigal	Stability data for Schmuff
11/18/92 fax	Edison	Schoenfelder - analyses tables
11/18/92 telecon	Schmuff	Responses to telecon questions
11/19/92 fax	Isom	Letter to investigators/T-IND
11/19/92 Amend 67	Feigal	Annotated version of proposed package insert
11/19/92 Amend 68	Feigal	Laboratory abnormality summaries for Dr. Edison
11/20/92 Amend 69	Feigal	Censored version of abbreviated EA

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #
12/17/92	N/A	PROMOTIONAL MATERIAL	Promotional Material Submitted to David Feigal (This Material Was Not Submitted to the NDA)	N/A
12/17/92	N/A	PROMOTIONAL MATERIAL	Video News Release # L129211 (Not Included)	N/A
12/17/92	N/A	PROMOTIONAL MATERIAL	Visual Aid # L119204	N/A
12/17/92	N/A	PROMOTIONAL MATERIAL	Journal Advertisement # 119213	N/A
12/17/92	N/A	PROMOTIONAL MATERIAL	Letter to Physicians	N/A
12/17/92	N/A	PROMOTIONAL MATERIAL	Letter to Pharmacist	N/A
12/17/92	N/A	PROMOTIONAL MATERIAL	Educational Pieces to be Distributed by Sales Force	N/A
12/22/92	N/A	PROMOTIONAL MATERIAL	Promotional Material Submitted to David Feigal (This Material Was Not Submitted to the NDA)	N/A
12/22/92	N/A	PROMOTIONAL MATERIAL	Video News Release # L129211	N/A
12/23/92	77.01	AMENDMENT	Revised Package Insert per Instructions Received by Ralph Lillie	217
12/23/92	N/A	FDA LETTER	Application Approved - Reference to 01/16/92 Submission & Amendments	217

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12/10/92	74.01	AMENDMENT	Response 14 - Specify How Capsules Containing Metal Particles are Visually Detected	217
12/10/92	74.01	AMENDMENT	Response 15 - Specify are Capsules Received Already Imprinted by Capsugel	217
12/10/92	74.01	AMENDMENT	Response 16 - Provide Description of Sampling Plans for all In-Prcess Controls	217
12/10/92	74.01	AMENDMENT	Response 17 - Specify Marketing Status for Blister Packaging Configuration	217
12/10/92	74.01	AMENDMENT	Response 18 - Provide Coupling Constants for Proton NMR Attributions & Enlarged Copy of NMR Spectrum	217
12/14/92	76.01	AMENDMENT	Revised Version of Package Insert	217
12/14/92	76.01	AMENDMENT	Responses to Dr. Norman Schmuff concerning CMC questions	217
12/14/92	76.01	AMENDMENT	1. Provide English Translation for Sampling Procedure F3001	217
12/14/92	76.01	AMENDMENT	2. With Regard to Sampling Procedures, How the 300 Capsules Are Selected	217
12/14/92	76.01	AMENDMENT	3. With Regard to 300 Capsules Sampled, How Many are Used for Testing, How Many Are Retained	217
12/14/92	76.01	AMENDMENT	4. Commit to USP Acceptance Criteria for Dissolution Method	217
12/14/92	76.01	AMENDMENT	5. Dissolution Specifications	217
12/14/92	76.01	AMENDMENT	6. Provide Certificate of Analysis for All Lots Produced to Date (Includes Manufacture & Lot Size)	217
12/15/92	75.01	AMENDMENT	Response to Dr. Schmuffs' Chemistry Request (12/15/92)	217
12/15/92	75.01	AMENDMENT	Revised Dissolution Specification from 80% to 75% Q	217
12/15/92	75.01	AMENDMENT	Time of Manufacture of Bulk Capsules to Completion Not to Exceed 90 Days	217
12/15/92	75.01	AMENDMENT	Stability Studies on Finished Product will be Initiated within 30 Days of QC Release	217
12/15/92	75.01	AMENDMENT	Expiration Date will be Calculated from date the Active Ingredient is Added to the Blend	217

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12/02/92	71.01	AMENDMENT	Table Presenting # of Events Included in Efficacy Analyses Data in WordPerfect Format, Requested by R. Edison	217
12/04/92	72.01	AMENDMENT	1. Response to FDA Request to Add Specific Adverse Experiences to Lists Included In Package Insert	217
12/04/92	72.01	AMENDMENT	2. Tabulation of Adv. Experiences Reported for Placebo Patients (less 1%), but not Reported for Rif Patients	217
12/04/92	72.01	AMENDMENT	3. Tables Presenting Results of Kaplan-Meier Analyses of Various Efficacy Variables	217
12/09/92	73.01	AMENDMENT	Response to Dr. Robin Edison Request for Additional Information	217
12/09/92	73.01	AMENDMENT	Rif vs Placebo Incidence Comparisons for Each AE & Demographic Summary Tables (Diskette Included)	217
12/10/92	74.01	AMENDMENT	Response to Dr. Schmuffs' FAX (12/08/92) and Telephone Request (12/10/92)	217
12/10/92	74.01	AMENDMENT	Response 1 - Provide Numbered Pages to all Future Submissions	217
12/10/92	74.01	AMENDMENT	Response 2 - Provide Additional Information Concerning Polymorphism	217
12/10/92	74.01	AMENDMENT	Response 3 - Provide Information Concerning Oxidation (03-048, 03-081)	217
12/10/92	74.01	AMENDMENT	Response 4 - Provide Stability Data for Lot 2/85	217
12/10/92	74.01	AMENDMENT	Response 5 - Provide Additional Information on the Container/Closure Used for Bulk Drug Substance	217
12/10/92	74.01	AMENDMENT	Response 6 - Provide In-Process Controls for Reaction Completion	217
12/10/92	74.01	AMENDMENT	Response 8 - Specify the Production Scale for Drug Substance	217
12/10/92	74.01	AMENDMENT	Response 9 - Specify the Production Scale for Drug Product	217
12/10/92	74.01	AMENDMENT	Response 11 - Provide a Completed Batch Record (Master & Completed)	217
12/10/92	74.01	AMENDMENT	Response 12 - Provide Description & Specifications for Post Blending In-Process Controls	217
12/10/92	74.01	AMENDMENT	Response 13 - Provide Description & Specifications for Material Controls	217

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10/30/92		FDA LETTER (FAX)	Written Comments concerning Chemistry Section of Package Insert	216
11/02/92		FDA LETTER (FAX)	Written Comments concerning Clinical Section of Package Insert	216
11/04/92	63.01	AMENDMENT	Response to Dr. Robin Edison Concerning the Use of Mycobutin in Pediatric Patients	216
11/09/92	64.01	AMENDMENT	Response to Dr. Robin Edison Concerning Patients with Grade 3/4 ANC And No 3/4 WBC	216
11/11/92	65.01	AMENDMENT	Revised Draft Package Insert	216
11/16/92	66.01	AMENDMENT	Updated Stability Data as Requested 11/13/92 by Dr. Norman Schmuff	216
11/19/92	67.01	AMENDMENT	Annotated Insert	216
11/19/92	67.01	AMENDMENT	References	216
11/19/92	67.01	AMENDMENT	Reference # 1	216
11/19/92	67.01	AMENDMENT	Reference # 8	216
11/19/92	67.01	AMENDMENT	Reference # 26	216
11/19/92	67.01	AMENDMENT	Reference # 29	216
11/19/92	67.01	AMENDMENT	Reference # 30	216
11/19/92	67.01	AMENDMENT	Reference # 41	216
11/19/92	67.01	AMENDMENT	Reference # 42	216
11/19/92	68.01	AMENDMENT	Summaries of Laboratory Abnormalities, as Requested by Robin Edison	216
11/20/92	69.01	AMENDMENT	Censored Version of the Abbreviated Enivronmental Assessment Releasable to Public	217
11/25/92	70.01	AMENDMENT	Response to Dr. Robin Edison Request for Updated Safety Results in WordPerfect Format	217

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09/15/92	53.01	AMENDMENT	Response 9 - Provide Analyses of Drug Effect on Total Fever (Statement of Criteria for Assessing Fever)	215
09/15/92	53.01	AMENDMENT	Response 10 - Provide Information for Labeling (Prevention of MAI Bacteremia or MAI Infection)	215
09/17/92	54.01	AMENDMENT	Revised Package Insert	215
10/01/92	55.01	AMENDMENT	Response to Dr. Robin Edisons' Request	216
10/01/92	55.01	AMENDMENT	Updated Tabulations	216
10/01/92	55.01	AMENDMENT	Diskettes Containing the Global Summary	216
10/01/92	55.01	AMENDMENT	Clinical Update that was Submitted in the Advisory Committee Backgrounder	216
10/01/92	56.01	AMENDMENT	Transfer of Responsibility of Product	216
10/12/92	57.01	AMENDMENT	Letter of Authorization to Install Computer Hardware/Software Associated with "Drag and Dictate"	216
10/15/92	58.01	AMENDMENT	Response to Dr. Grahams' Comment Concerning HPLC Method for Drug Substance	216
10/15/92	59.01	AMENDMENT	Response to Dr. Robin Edisons' Request	216
10/15/92	59.01	AMENDMENT	Updates of the Hematologic and Liver Toxicity Analyses	216
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05/01/92	21.02	AMENDMENT	Patient # 019-006	195
05/01/92	21.02	AMENDMENT	Patient # 019-013	195
05/01/92	21.02	AMENDMENT	Patient # 019-019	195
05/01/92	21.02	AMENDMENT	Patient # 020-004	195
05/01/92	21.02	AMENDMENT	Patient # 020-012	195
05/01/92	21.02	AMENDMENT	Patient # 021-005	195
05/01/92	21.02	AMENDMENT	Patient # 021-017	195
05/01/92	21.02	AMENDMENT	Patient # 023-001	195
05/01/92	21.02	AMENDMENT	Patient # 023-028	195
05/01/92	21.02	AMENDMENT	Patient # 023-029	195

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #
05/01/92	21.02	AMENDMENT	Patient # 023-035	195
05/01/92	21.02	AMENDMENT	Patient # 024-005	195
05/01/92	21.02	AMENDMENT	Patient # 028-006	195
05/01/92	21.02	AMENDMENT	Patient # 028-008	195
05/01/92	21.02	AMENDMENT	Patient # 028-010	195
05/01/92	21.02	AMENDMENT	Patient # 037-004	195
05/01/92	21.02	AMENDMENT	Patient # 038-022	195
05/01/92	21.02	AMENDMENT	Patient # 042-010	195
05/01/92	21.02	AMENDMENT	Patient # 042-011	195
05/01/92	21.02	AMENDMENT	Case Report Forms - CS# 087027	195
05/01/92	21.02	AMENDMENT	Patient # 001-005	195
05/01/92	21.02	AMENDMENT	Patient # 001-007	195
05/01/92	21.02	AMENDMENT	Patient # 001-010	195
05/01/92	21.02	AMENDMENT	Patient # 004-005	195
05/01/92	21.02	AMENDMENT	Patient # 004-006	195
05/01/92	21.02	AMENDMENT	Patient # 004-020	195
05/01/92	21.02	AMENDMENT	Patient # 007-006	195
05/01/92	21.02	AMENDMENT	Patient # 007-024	195

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05/01/92	21.02	AMENDMENT	Patient # 007-025	195
05/01/92	21.02	AMENDMENT	Patient # 008-002	195
05/01/92	21.02	AMENDMENT	Patient # 009-003	195
05/01/92	21.02	AMENDMENT	Patient # 009-014	195
05/01/92	21.02	AMENDMENT	Patient # 009-018	195
05/01/92	21.02	AMENDMENT	Patient # 009-025	195
05/01/92	21.02	AMENDMENT	Patient # 009-028	195
05/01/92	21.02	AMENDMENT	Patient # 009-029	195
05/01/92	21.02	AMENDMENT	Patient # 009-033	195
05/01/92	21.02	AMENDMENT	Patient # 009-041	195
05/01/92	21.02	AMENDMENT	Patient # 010-004	195
05/01/92	21.02	AMENDMENT	Patient # 010-012	195
05/01/92	21.02	AMENDMENT	Patient # 010-013	195
05/01/92	21.02	AMENDMENT	Patient # 012-022	195
05/01/92	21.02	AMENDMENT	Patient # 016-002	195
05/01/92	21.02	AMENDMENT	Patient # 018-005	195
05/01/92	21.02	AMENDMENT	Patient # 018-010	195
05/01/92	21.02	AMENDMENT	Patient # 018-011	195

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #
05/01/92	21.02	AMENDMENT	Patient # 019-002	195
05/01/92	21.02	AMENDMENT	Patient # 023-003	195
05/01/92	21.01	AMENDMENT	Cover Letter, 356 H Form & Index	196
05/01/92	21.01	AMENDMENT	MAC Event Patients - Updated	196
05/01/92	21.01	AMENDMENT	Case Report Forms - CS# 087023	196
05/01/92	21.01	AMENDMENT	Patient # 001-002	196
05/01/92	21.01	AMENDMENT	Patient # 001-017	196
05/01/92	21.01	AMENDMENT	Patient # 001-036	196
05/01/92	21.01	AMENDMENT	Patient # 001-037	196
05/01/92	21.01	AMENDMENT	Patient # 001-038	196
05/01/92	21.01	AMENDMENT	Patient # 001-048	196
05/01/92	21.01	AMENDMENT	Patient # 001-050	196
05/01/92	21.01	AMENDMENT	Patient # 001-055	196
05/01/92	21.01	AMENDMENT	Patient # 001-068	196
05/01/92	21.01	AMENDMENT	Patient # 001-072	196
05/01/92	21.01	AMENDMENT	Patient # 003-007	196
05/01/92	21.01	AMENDMENT	Patient # 004-001	196
05/01/92	21.01	AMENDMENT	Patient # 004-002	196

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DATE	#	TYPE	LETTER SUBJECT	VOL #
05/01/92	21.01	AMENDMENT	Patient # 004-004	196
05/01/92	21.01	AMENDMENT	Patient # 004-007	196
05/01/92	21.01	AMENDMENT	Patient # 004-010	196
05/01/92	21.01	AMENDMENT	Patient # 004-017	196
05/01/92	21.01	AMENDMENT	Patient # 004-019	196
05/01/92	21.01	AMENDMENT	Patient # 004-022	196
05/01/92	21.01	AMENDMENT	Patient # 004-038	196
05/01/92	21.01	AMENDMENT	Patient # 005-004	196
05/01/92	21.01	AMENDMENT	Patient # 007-001	196
05/01/92	21.01	AMENDMENT	Patient # 007-003	196
05/01/92	21.01	AMENDMENT	Patient # 007-007	196
05/01/92	21.01	AMENDMENT	Patient # 007-017	196
05/01/92	21.01	AMENDMENT	Patient # 007-018	196
05/01/92	21.01	AMENDMENT	Patient # 008-001	196
05/01/92	21.01	AMENDMENT	Patient # 008-003	196
05/01/92	21.01	AMENDMENT	Patient # 008-010	196
05/01/92	21.01	AMENDMENT	Patient # 009-001	196
05/01/92	21.01	AMENDMENT	Patient # 009-002	196

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #
05/01/92	21.01	AMENDMENT	Patient # 009-028	196
05/01/92	21.01	AMENDMENT	Patient # 009-03C	196
05/01/92	21.01	AMENDMENT	Patient # 009-033	196
05/01/92	21.01	AMENDMENT	Patient # 009-042	196
05/01/92	21.01	AMENDMENT	Patient # 009-045	196
05/01/92	21.01	AMENDMENT	Patient # 009-048	196
05/01/92		FDA LETTER (fax)	Percent of Cultures reported Positive/one-time vs repeat positives	196
05/05/92	22.01	AMENDMENT	Clinical	197
05/05/92	22.01	AMENDMENT	Response to 1-5, 8, Part 2 of 4/1/92 Request	197
05/05/92	22.01	AMENDMENT	MAC Bacteremia Incidence Rates	197
05/05/92	22.01	AMENDMENT	Proc Tabulate Output	197
05/05/92	22.02	AMENDMENT	Statistical	197
05/05/92	22.02	AMENDMENT	MAC Bacteremia Incidence Rates	197
05/05/92	22.02	AMENDMENT	Proc Tabulate Output	197
05/06/92	23.08	AMENDMENT	Final Report - CS# 087027 (Continued)	198
05/06/92	23.08	AMENDMENT	Appendix VII - Patient Data Tabulations (Continued)	198
05/06/92	23.07	AMENDMENT	Final Report - CS# 087027 (Continued)	199
05/06/92	23.07	AMENDMENT	Appendix II - Protocol, Sample Case Report Form, and Amendment (Continued)	199

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/30/92	20	AMENDMENT	Response to Dr. Kammerman (04/01/92 FAX) Continued	193	20.02
04/30/92	20	AMENDMENT	Attachment 2 - Request for Efficacy Analyses	193	20.02
04/30/92	20	AMENDMENT	Response to Dr. Kammerman (04/01/92 FAX)	194	20.01
04/30/92	20	AMENDMENT	Attachment 1 - Request for Info. by Site, Efficacy Results for Individual Centers	194	20.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/16/92	15	AMENDMENT	Analyses that Adjusted for Each Corvariate in an Univariate Fashion	190	15.01
04/16/92	15	AMENDMENT	Analyses that were Used to Stop Study 087023	190	15.01
04/24/92	16	AMENDMENT	Responses to Dr. Edison Request	191	16.01
04/24/92	16	AMENDMENT	Information Concerning Subjects who were Randomized After their 1st Dose	191	16.01
04/24/92	16	AMENDMENT	Documentation of Culture Dates Used in the Study Efficacy Analyses	191	16.01
04/24/92	16	AMENDMENT	New SAS Data Set - Information Regarding Adverse Experiences Collected	191	16.01
04/24/92	17	AMENDMENT	Response to Dr. Kammerman Request	191	17.01
04/24/92	17	AMENDMENT	Summary Tables of Disposition of Patients Entered	191	17.01
04/28/92	18	AMENDMENT	Response to Dr. Edison - Dates of Randomization & Cultures (Experiencing at Least 1 Positive Blood Culture)	191	18.01
04/29/92	19	AMENDMENT	Response to Dr. Edison Request for Information Concerning Changed MetPath Blood Culture Reports	192	19.01
04/29/92	19	AMENDMENT	Synopsis	192	19.01
04/29/92	19	AMENDMENT	Appendix A - Bactec Specimen Run #A	192	19.01
04/29/92	19	AMENDMENT	Appendix B - Bactec Specimen Run #B	192	19.01
04/29/92	19	AMENDMENT	Appendix C - Bactec Specimen Run #C	192	19.01
04/29/92	19	AMENDMENT	Appendix D - Bactec Specimen Run #D	192	19.01
04/29/92	19	AMENDMENT	Appendix E - Bactec Specimen Run #E	192	19.01
04/29/92	19	AMENDMENT	Appendix F - Bactec Specimen Run #F	192	19.01
04/29/92	19	AMENDMENT	Appendix G - Reprint of Article on Genetic Typing of Mycobacteria	192	19.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	187	13.03
04/15/92	13	AMENDMENT	Patient # 009-007	187	13.03
04/15/92	13	AMENDMENT	Patient # 009-020	187	13.03
04/15/92	13	AMENDMENT	Patient # 009-047	187	13.03
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	188	13.02
04/15/92	13	AMENDMENT	Patient # 001-081	188	13.02
04/15/92	13	AMENDMENT	Patient # 004-006	188	13.02
04/15/92	13	AMENDMENT	Patient # 004-028	188	13.02
04/15/92	13	AMENDMENT	Patient # 007-013	188	13.02
04/15/92	13	AMENDMENT	Cover Letter, 356 H Form & Index	189	13.01
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087023	189	13.01
04/15/92	13	AMENDMENT	Patient # 001-007	189	13.01
04/15/92	13	AMENDMENT	Patient # 001-022	189	13.01
04/15/92	13	AMENDMENT	Patient # 001-057	189	13.01
04/16/92	14	AMENDMENT	Responses to Dr. Edison Request	190	14.01
04/16/92	14	AMENDMENT	Survival Update Forms used During the Data Entry Process	190	14.01
04/16/92	15	AMENDMENT	Responses to Dr. Kammerman Request	190	15.01
04/16/92	15	AMENDMENT	Analyses Contained in the NDA that Exclude Post-Open Label Events	190	15.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/15/92	13	AMENDMENT	Patient # 010-003	182	13.08
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	183	13.07
04/15/92	13	AMENDMENT	Patient # 042-004	183	13.07
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087027	183	13.07
04/15/92	13	AMENDMENT	Patient # 001-004	183	13.07
04/15/92	13	AMENDMENT	Patient # 004-016	183	13.07
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	184	13.06
04/15/92	13	AMENDMENT	Patient # 023-034	184	13.06
04/15/92	13	AMENDMENT	Patient # 023-046	184	13.06
04/15/92	13	AMENDMENT	Patient # 038-006	184	13.06
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	185	13.05
04/15/92	13	AMENDMENT	Patient # 021-010	185	13.05
04/15/92	13	AMENDMENT	Patient # 023-003	185	13.05
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	186	13.04
04/15/92	13	AMENDMENT	Patient # 009-081	186	13.04
04/15/92	13	AMENDMENT	Patient # 015-012	186	13.04
04/15/92	13	AMENDMENT	Patient # 019-010	186	13.04
04/15/92	13	AMENDMENT	Patient # 019-027	186	13.04

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04/15/92	13	AMENDMENT	Patient # 503-023	179	13.11
04/15/92	13	AMENDMENT	Patient # 503-048	179	13.11
04/15/92	13	AMENDMENT	Patient # 507-001	179	13.11
04/15/92	13	AMENDMENT	Patient # 512-012	179	13.11
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	180	13.10
04/15/92	13	AMENDMENT	Patient # 024-012	180	13.10
04/15/92	13	AMENDMENT	Patient # 025-008	180	13.10
04/15/92	13	AMENDMENT	Patient # 028-013	180	13.10
04/15/92	13	AMENDMENT	Patient # 039-011	180	13.10
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	181	13.09
04/15/92	13	AMENDMENT	Patient # 012-011	181	13.09
04/15/92	13	AMENDMENT	Patient # 018-008	181	13.09
04/15/92	13	AMENDMENT	Patient # 018-016	181	13.09
04/15/92	13	AMENDMENT	Patient # 023-016	181	13.09
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	182	13.08
04/15/92	13	AMENDMENT	Patient # 007-019	182	13.08
04/15/92	13	AMENDMENT	Patient # 009-010	182	13.08
04/15/92	13	AMENDMENT	Patient # 009-021	182	13.08

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/08/92	11	AMENDMENT	Patient # 004-006	175	11.03
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	176	11.02
04/08/92	11	AMENDMENT	MAC Event Patients - Updated (Continued)	176	11.02
04/08/92	11	AMENDMENT	Patient # 028-007	176	11.02
04/08/92	11	AMENDMENT	Patient # 041-008	176	11.02
04/08/92	11	AMENDMENT	Post Open Label - MAC Event Patients	176	11.02
04/08/92	11	AMENDMENT	Patient # 003-001	176	11.02
04/08/92	11	AMENDMENT	Cover Letter, 356 H Form & Index	177	11.01
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087023	177	11.01
04/08/92	11	AMENDMENT	MAC Event Patients - Updated	177	11.01
04/08/92	11	AMENDMENT	Patient # 001-058	177	11.01
04/08/92	11	AMENDMENT	Patient # 001-080	177	11.01
04/08/92	11	AMENDMENT	Patient # 004-017	177	11.01
04/14/92	12	AMENDMENT	Responses to Dr. Edison's Request	178	12.01
04/14/92	12	AMENDMENT	Information Concerning Methodologies Used by Provincial Laboratory of Northern Alberta	178	12.01
04/14/92	12	AMENDMENT	Information Concerning a Description of Revisions to Case Report Forms for CS# 087023 & 087027	178	12.01
04/15/92	13	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	179	13.11
04/15/92	13	AMENDMENT	Patient # 503-004	179	13.11

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	172	11.06
04/08/92	11	AMENDMENT	Post Open Label - MAC Event Patients (Continued)	172	11.06
04/08/92	11	AMENDMENT	Patient # 019-031	172	11.06
04/08/92	11	AMENDMENT	Patient # 021-018	172	11.06
04/08/92	11	AMENDMENT	Patient # 025-006	172	11.06
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	173	11.05
04/08/92	11	AMENDMENT	Post Open Label - MAC Event Patients (Continued)	173	11.05
04/08/92	11	AMENDMENT	Patient # 009-084	173	11.05
04/08/92	11	AMENDMENT	Patient # 015-009	173	11.05
04/08/92	11	AMENDMENT	Patient # 019-029	173	11.05
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	174	11.04
04/08/92	11	AMENDMENT	Post Open Label - MAC Event Patients (Continued)	174	11.04
04/08/92	11	AMENDMENT	Patient # 004-030	174	11.04
04/08/92	11	AMENDMENT	Patient # 006-001	174	11.04
04/08/92	11	AMENDMENT	Patient # 009-054	174	11.04
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	175	11.03
04/08/92	11	AMENDMENT	Post Open Label - MAC Event Patients (Continued)	175	11.03
04/08/92	11	AMENDMENT	Patient # 003-004	175	11.03

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/08/92	11	AMENDMENT	MAC Event Patients - Updated (Continued)	169	11.09
04/08/92	11	AMENDMENT	Patient # 018-024	169	11.09
04/08/92	11	AMENDMENT	Patient # 018-034	169	11.09
04/08/92	11	AMENDMENT	Patient # 018-038	169	11.09
04/08/92	11	AMENDMENT	Patient # 019-003	169	11.09
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	170	11.08
04/08/92	11	AMENDMENT	MAC Event Patients - Updated (Continued)	170	11.08
04/08/92	11	AMENDMENT	Patient # 009-029	170	11.08
04/08/92	11	AMENDMENT	Patient # 009-033	170	11.08
04/08/92	11	AMENDMENT	Patient # 012-021	170	11.08
04/08/92	11	AMENDMENT	Patient # 018-022	170	11.08
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	171	11.07
04/08/92	11	AMENDMENT	Post Open Label - MAC Event Patients (Continued)	171	11.07
04/08/92	11	AMENDMENT	Patient # 024-009	171	11.07
04/08/92	11	AMENDMENT	Patient # 025-006	171	11.07
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087027	171	11.07
04/08/92	11	AMENDMENT	MAC Event Patients - Updated	171	11.07
04/08/92	11	AMENDMENT	Patient # 001-019	171	11.07

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
04/06/92	10	AMENDMENT	Correspondence to Dr. Edison	165	10.01
04/06/92	10	AMENDMENT	Expanded Version of Rifabutin SAS Data Set	165	10.01
04/06/92	10	AMENDMENT	Case Report Form - Corrections/Additions	165	10.01
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	166	11.12
04/08/92	11	AMENDMENT	Post Open Label - MAC Event Patients	166	11.12
04/08/92	11	AMENDMENT	Patient # 003-008	166	11.12
04/08/92	11	AMENDMENT	Patient # 009-005	166	11.12
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	167	11.11
04/08/92	11	AMENDMENT	MAC Event Patients - Updated (Continued)	167	11.11
04/08/92	11	AMENDMENT	Patient # 036-002	167	11.11
04/08/92	11	AMENDMENT	Patient # 503-017	167	11.11
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	168	11.10
04/08/92	11	AMENDMENT	MAC Event Patients - Updated (Continued)	168	11.10
04/08/92	11	AMENDMENT	Patient # 024-005	168	11.10
04/08/92	11	AMENDMENT	Patient # 024-014	168	11.10
04/08/92	11	AMENDMENT	Patient # 028-014	168	11.10
04/08/92	11	AMENDMENT	Patient # 035-004	168	11.10
04/08/92	11	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	169	11.09

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/30/92	8	AMENDMENT	Patient # 005-005	163	8.01
03/30/92	8	AMENDMENT	Patient # 006-006	163	8.01
03/30/92	8	AMENDMENT	Patient # 008-011	163	8.01
03/31/92	9	AMENDMENT	Response to Dr. Edison	164	9.01
03/31/92	9	AMENDMENT	Letter to Dr. Edison	164	9.01
03/31/92	9	AMENDMENT	MAC vs Non-MAC (Non-Matched)	164	9.01
03/31/92	9	AMENDMENT	MAC vs Non-MAC (Matched)	164	9.01
03/31/92	9	AMENDMENT	Updated MAC vs Non-MAC (Non-Matched)	164	9.01
03/31/92	9	AMENDMENT	Updated MAC vs Non-MAC (Matched)	164	9.01
04/01/92		FDA LETTER (FAX)	CLINICAL & STATISTICAL REQUESTS FOR DESCRIPTIVE INFORMATION-ADDITIONAL ANALYSIS	164	N/A
04/02/92	N/A	DESK COPY	Cover Letter & 356 H Form	Not Submitte	
04/02/92	N/A	DESK COPY	List of Investigators - 087023 & 087027	Not Submitte	
04/02/92	N/A	DESK COPY	Protocol - CS# 087023-999	Not Submitte	
04/02/92	N/A	DESK COPY	Protocol - CS# 087027-999	Not Submitte	
04/02/92	N/A	DESK COPY	Protocol - CS# 087027-999 (Canada)	Not Submitte	
04/02/92	N/A	DESK COPY	Patient Groupings/Table RE1	Not Submitte	
04/02/92	N/A	DESK COPY	Adverse Experience/Table S1	Not Submitte	
04/06/92	10	AMENDMENT	Response to Dr. Edison	165	10.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/30/92	8	AMENDMENT	Patient # 019-020	161	8.03
03/30/92	8	AMENDMENT	Patient # 023-004	161	8.03
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	161	8.03
03/30/92	8	AMENDMENT	Patient # 008-015	162	8.02
03/30/92	8	AMENDMENT	Patient # 008-027	162	8.02
03/30/92	8	AMENDMENT	Patient # 008-030	162	8.02
03/30/92	8	AMENDMENT	Patient # 009-044	162	8.02
03/30/92	8	AMENDMENT	Patient # 009-059	162	8.02
03/30/92	8	AMENDMENT	Patient # 009-062	162	8.02
03/30/92	8	AMENDMENT	Patient # 009-075	162	8.02
03/30/92	8	AMENDMENT	Patient # 009-079	162	8.02
03/30/92	8	AMENDMENT	Cover Letter, 356 H Form and Index	163	8.01
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087023	163	8.01
03/30/92	8	AMENDMENT	Patient # 001-026	163	8.01
03/30/92	8	AMENDMENT	Patient # 001-063	163	8.01
03/30/92	8	AMENDMENT	Patient # 001-071	163	8.01
03/30/92	8	AMENDMENT	Patient # 001-079	163	8.01
03/30/92	8	AMENDMENT	Patient # 005-001	163	8.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/30/92	8	AMENDMENT	Patient # 023-044	159	8.05
03/30/92	8	AMENDMENT	Patient # 024-003	159	8.05
03/30/92	8	AMENDMENT	Patient # 024-007	159	8.05
03/30/92	8	AMENDMENT	Patient # 024-014	159	8.05
03/30/92	8	AMENDMENT	Patient # 025-007	159	8.05
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	159	8.05
03/30/92	8	AMENDMENT	Patient # 023-005	160	8.04
03/30/92	8	AMENDMENT	Patient # 023-008	160	8.04
03/30/92	8	AMENDMENT	Patient # 023-009	160	8.04
03/30/92	8	AMENDMENT	Patient # 023-023	160	8.04
03/30/92	8	AMENDMENT	Patient # 023-026	160	8.04
03/30/92	8	AMENDMENT	Patient # 023-033	160	8.04
03/30/92	8	AMENDMENT	Patient # 023-036	160	8.04
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	160	8.04
03/30/92	8	AMENDMENT	Patient # 012-004	161	8.03
03/30/92	8	AMENDMENT	Patient # 013-001	161	8.03
03/30/92	8	AMENDMENT	Patient # 014-001	161	8.03
03/30/92	8	AMENDMENT	Patient # 015-005	161	8.03

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/30/92	8	AMENDMENT	Patient # 009-024	156	8.08
03/30/92	8	AMENDMENT	Patient # 012-002	156	8.08
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087027	157	8.07
03/30/92	8	AMENDMENT	Patient # 001-006	157	8.07
03/30/92	8	AMENDMENT	Patient # 001-011	157	8.07
03/30/92	8	AMENDMENT	Patient # 004-003	157	8.07
03/30/92	8	AMENDMENT	Patient # 004-008	157	8.07
03/30/92	8	AMENDMENT	Patient # 004-010	157	8.07
03/30/92	8	AMENDMENT	Patient # 004-019	157	8.07
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	157	8.07
03/30/92	8	AMENDMENT	Patient # 028-007	158	8.06
03/30/92	8	AMENDMENT	Patient # 042-002	158	8.06
03/30/92	8	AMENDMENT	Patient # 042-005	158	8.06
03/30/92	8	AMENDMENT	Patient # 042-006	158	8.06
03/30/92	8	AMENDMENT	Patient # 044-005	158	8.06
03/30/92	8	AMENDMENT	Patient # 046-008	158	8.06
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	158	8.06
03/30/92	8	AMENDMENT	Patient # 023-041	159	8.05

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/30/92	8	AMENDMENT	Patient # 031-003	154	8.10
03/30/92	8	AMENDMENT	Patient # 033-002	154	8.10
03/30/92	8	AMENDMENT	Patient # 033-004	154	8.10
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	155	8.09
03/30/92	8	AMENDMENT	Patient # 012-012	155	8.09
03/30/92	8	AMENDMENT	Patient # 012-013	155	8.09
03/30/92	8	AMENDMENT	Patient # 016-004	155	8.09
03/30/92	8	AMENDMENT	Patient # 018-002	155	8.09
03/30/92	8	AMENDMENT	Patient # 018-009	155	8.09
03/30/92	8	AMENDMENT	Patient # 018-021	155	8.09
03/30/92	8	AMENDMENT	Patient # 018-025	155	8.09
03/30/92	8	AMENDMENT	Patient # 018-037	155	8.09
03/30/92	8	AMENDMENT	Patient # 020-008	155	8.09
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	156	8.08
03/30/92	8	AMENDMENT	Patient # 007-003	156	8.08
03/30/92	8	AMENDMENT	Patient # 007-009	156	8.08
03/30/92	8	AMENDMENT	Patient # 008-004	156	8.08
03/30/92	8	AMENDMENT	Patient # 009-015	156	8.08

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/30/92	8	AMENDMENT	Patient # 504-011	152	8.12
03/30/92	8	AMENDMENT	Patient # 505-008	152	8.12
03/30/92	8	AMENDMENT	Patient # 509-003	152	8.12
03/30/92	8	AMENDMENT	Patient # 510-001	152	8.12
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	153	8.11
03/30/92	8	AMENDMENT	Patient # 039-002	153	8.11
03/30/92	8	AMENDMENT	Patient # 039-006	153	8.11
03/30/92	8	AMENDMENT	Patient # 039-008	153	8.11
03/30/92	8	AMENDMENT	Patient # 039-012	153	8.11
03/30/92	8	AMENDMENT	Patient # 039-013	153	8.11
03/30/92	8	AMENDMENT	Patient # 501-007	153	8.11
03/30/92	8	AMENDMENT	Patient # 503-007	153	8.11
03/30/92	8	AMENDMENT	Patient # 503-036	153	8.11
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	154	8.10
03/30/92	8	AMENDMENT	Patient # 023-014	154	8.10
03/30/92	8	AMENDMENT	Patient # 023-020	154	8.10
03/30/92	8	AMENDMENT	Patient # 024-003	154	8.10
03/30/92	8	AMENDMENT	Patient # 024-009	154	8.10

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/23/92	6	AMENDMENT	RL Tables	150	6.01
03/23/92	6	AMENDMENT	RE1 Tables	150	6.01
03/23/92	6	AMENDMENT	ZA1 Tables	150	6.01
03/23/92		FDA LETTER	New Review Date 9/13/92, Reference made to Submission Dated 03/17/92 Considered Major Amendment Not Minor	150	N/A
03/25/92	7	AMENDMENT	Responses to Dr. R. Edison	151	7.01
03/25/92	7	AMENDMENT	Letter to Dr. R. Edison	151	7.01
03/25/92	7	AMENDMENT	TD Tables and Figures	151	7.01
03/25/92	7	AMENDMENT	ZA5 Tables	151	7.01
03/25/92	7	AMENDMENT	ZA6 Tables	151	7.01
03/25/92	7	AMENDMENT	Susceptibility Reports	151	7.01
03/25/92	7	AMENDMENT	Clinical Monitoring	151	7.01
03/25/92	7	AMENDMENT	Met Path Laboratories Information	151	7.01
03/25/92	7	AMENDMENT	Attachment I	151	7.01
03/25/92	7	AMENDMENT	Attachment II	151	7.01
03/25/92	7	AMENDMENT	Attachment III	151	7.01
03/30/92		FDA LETTER (FAX)	Request for additional CFRs for all cases of MAC event occuring on open label	151	N/A
03/30/92	8	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	152	8.12
03/30/92	8	AMENDMENT	Patient # 504-008	152	8.12

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/23/92	5	AMENDMENT	Patient # 001-035	147	5.03
03/23/92	5	AMENDMENT	Patient # 001-041	147	5.03
03/23/92	5	AMENDMENT	Patient # 001-045	147	5.03
03/23/92	5	AMENDMENT	Patient # 001-053	147	5.03
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	148	5.02
03/23/92	5	AMENDMENT	Patient # 001-011	148	5.02
03/23/92	5	AMENDMENT	Patient # 001-012	148	5.02
03/23/92	5	AMENDMENT	Patient # 001-014	148	5.02
03/23/92	5	AMENDMENT	Patient # 001-016	148	5.02
03/23/92	5	AMENDMENT	Cover Letter, 356 H Form and Index	149	5.01
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023	149	5.01
03/23/92	5	AMENDMENT	Patient # 001-001	149	5.01
03/23/92	5	AMENDMENT	Patient # 001-003	149	5.01
03/23/92	5	AMENDMENT	Patient # 001-005	149	5.01
03/23/92	5	AMENDMENT	Patient # 001-008	149	5.01
03/23/92	6	AMENDMENT	Responses to Dr. R. Edison	150	6.01
03/23/92	6	AMENDMENT	Letter to Dr. Edison	150	6.01
03/23/92	6	AMENDMENT	EX Tables	150	6.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/23/92	5	AMENDMENT	Patient # 021-004	144	5.06
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	145	5.05
03/23/92	5	AMENDMENT	Patient # 009-039	145	5.05
03/23/92	5	AMENDMENT	Patient # 009-057	145	5.05
03/23/92	5	AMENDMENT	Patient # 009-069	145	5.05
03/23/92	5	AMENDMENT	Patient # 014-002	145	5.05
03/23/92	5	AMENDMENT	Patient # 015-003	145	5.05
03/23/92	5	AMENDMENT	Patient # 019-002	145	5.05
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	146	5.06
03/23/92	5	AMENDMENT	Patient # 003-008	146	5.06
03/23/92	5	AMENDMENT	Patient # 004-027	146	5.06
03/23/92	5	AMENDMENT	Patient # 008-002	146	5.06
03/23/92	5	AMENDMENT	Patient # 008-008	146	5.06
03/23/92	5	AMENDMENT	Patient # 008-013	146	5.06
03/23/92	5	AMENDMENT	Patient # 009-015	146	5.06
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	147	5.03
03/23/92	5	AMENDMENT	Patient # 001-033	147	5.03
03/23/92	5	AMENDMENT	Patient # 001-034	147	5.03

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	142	5.08
03/23/92	5	AMENDMENT	Patient # 024-002	142	5.08
03/23/92	5	AMENDMENT	Patient # 028-011	142	5.08
03/23/92	5	AMENDMENT	Patient # 038-002	142	5.08
03/23/92	5	AMENDMENT	Patient # 038-005	142	5.08
03/23/92	5	AMENDMENT	Patient # 038-012	142	5.08
03/23/92	5	AMENDMENT	Patient # 038-031	142	5.08
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	143	5.07
03/23/92	5	AMENDMENT	Patient # 021-014	143	5.07
03/23/92	5	AMENDMENT	Patient # 021-016	143	5.07
03/23/92	5	AMENDMENT	Patient # 023-011	143	5.07
03/23/92	5	AMENDMENT	Patient # 023-013	143	5.07
03/23/92	5	AMENDMENT	Patient # 023-020	143	5.07
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	144	5.06
03/23/92	5	AMENDMENT	Patient # 019-005	144	5.06
03/23/92	5	AMENDMENT	Patient # 019-021	144	5.06
03/23/92	5	AMENDMENT	Patient # 019-035	144	5.06
03/23/92	5	AMENDMENT	Patient # 021-001	144	5.06

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/23/92	5	AMENDMENT	Patient # 010-006	139	5.11
03/23/92	5	AMENDMENT	Patient # 010-022	139	5.11
03/23/92	5	AMENDMENT	Patient # 018-003	139	5.11
03/23/92	5	AMENDMENT	Patient # 018-006	139	5.11
03/23/92	5	AMENDMENT	Patient # 018-007	139	5.11
03/23/92	5	AMENDMENT	Patient # 023-009	139	5.11
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	140	5.10
03/23/92	5	AMENDMENT	Patient # 007-020	140	5.10
03/23/92	5	AMENDMENT	Patient # 008-006	140	5.10
03/23/92	5	AMENDMENT	Patient # 009-001	140	5.10
03/23/92	5	AMENDMENT	Patient # 009-026	140	5.10
03/23/92	5	AMENDMENT	Patient # 010-005	140	5.10
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087027	141	5.09
03/23/92	5	AMENDMENT	Patient # 001-001	141	5.09
03/23/92	5	AMENDMENT	Patient # 003-007	141	5.09
03/23/92	5	AMENDMENT	Patient # 004-009	141	5.09
03/23/92	5	AMENDMENT	Patient # 004-018	141	5.09
03/23/92	5	AMENDMENT	Patient # 004-021	141	5.09

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Patient # 001-036	136	4.01
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	137	5.13
03/23/92	5	AMENDMENT	Patient # 503-005	137	5.13
03/23/92	5	AMENDMENT	Patient # 503-014	137	5.13
03/23/92	5	AMENDMENT	Patient # 503-020	137	5.13
03/23/92	5	AMENDMENT	Patient # 503-030	137	5.13
03/23/92	5	AMENDMENT	Patient # 508-001	137	5.13
03/23/92	5	AMENDMENT	Patient # 510-002	137	5.13
03/23/92	5	AMENDMENT	Patient # 510-004	137	5.13
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	138	5.12
03/23/92	5	AMENDMENT	Patient # 025-004	138	5.12
03/23/92	5	AMENDMENT	Patient # 025-006	138	5.12
03/23/92	5	AMENDMENT	Patient # 031-001	138	5.12
03/23/92	5	AMENDMENT	Patient # 035-002	138	5.12
03/23/92	5	AMENDMENT	Patient # 035-003	138	5.12
03/23/92	5	AMENDMENT	Patient # 036-003	138	5.12
03/23/92	5	AMENDMENT	Patient # 039-003	138	5.12
03/23/92	5	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	139	5.11

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Patient # 004-003	133	4.04
03/17/92	4	AMENDMENT	Patient # 004-004	133	4.04
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	134	4.03
03/17/92	4	AMENDMENT	Patient # 001-050	134	4.03
03/17/92	4	AMENDMENT	Patient # 001-055	134	4.03
03/17/92	4	AMENDMENT	Patient # 001-068	134	4.03
03/17/92	4	AMENDMENT	Patient # 001-072	134	4.03
03/17/92	4	AMENDMENT	Patient # 003-007	134	4.03
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	135	4.02
03/17/92	4	AMENDMENT	Patient # 001-037	135	4.02
03/17/92	4	AMENDMENT	Patient # 001-038	135	4.02
03/17/92	4	AMENDMENT	Patient # 001-040	135	4.02
03/17/92	4	AMENDMENT	Patient # 001-048	135	4.02
03/17/92	4	AMENDMENT	Cover Letter, 356 H Form and Index	136	4.01
03/17/92	4	AMENDMENT	Case Report Forms CS# 087023	136	4.01
03/17/92	4	AMENDMENT	Patient # 001-002	136	4.01
03/17/92	4	AMENDMENT	Patient # 001-017	136	4.01
03/17/92	4	AMENDMENT	Patient # 001-030	136	4.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Patient # 007-017	130	4.07
03/17/92	4	AMENDMENT	Patient # 007-018	130	4.07
03/17/92	4	AMENDMENT	Patient # 008-001	130	4.07
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	131	4.06
03/17/92	4	AMENDMENT	Patient # 004-038	131	4.06
03/17/92	4	AMENDMENT	Patient # 005-004	131	4.06
03/17/92	4	AMENDMENT	Patient # 006-002	131	4.06
03/17/92	4	AMENDMENT	Patient # 007-001	131	4.06
03/17/92	4	AMENDMENT	Patient # 007-003	131	4.06
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	132	4.05
03/17/92	4	AMENDMENT	Patient # 004-007	132	4.05
03/17/92	4	AMENDMENT	Patient # 004-010	132	4.05
03/17/92	4	AMENDMENT	Patient # 004-019	132	4.05
03/17/92	4	AMENDMENT	Patient # 004-022	132	4.05
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	133	4.04
03/17/92	4	AMENDMENT	Patient # 003-010	133	4.04
03/17/92	4	AMENDMENT	Patient # 004-001	133	4.04
03/17/92	4	AMENDMENT	Patient # 004-002	133	4.04

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Patient # 009-080	126	4.11
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	127	4.10
03/17/92	4	AMENDMENT	Patient # 009-033	127	4.10
03/17/92	4	AMENDMENT	Patient # 009-037	127	4.10
03/17/92	4	AMENDMENT	Patient # 009-040	127	4.10
03/17/92	4	AMENDMENT	Patient # 009-042	127	4.10
03/17/92	4	AMENDMENT	Patient # 009-045	127	4.10
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	128	4.09
03/17/92	4	AMENDMENT	Patient # 009-002	128	4.09
03/17/92	4	AMENDMENT	Patient # 009-028	128	4.09
03/17/92	4	AMENDMENT	Patient # 009-030	128	4.09
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	129	4.08
03/17/92	4	AMENDMENT	Patient # 008-003	129	4.08
03/17/92	4	AMENDMENT	Patient # 008-010	129	4.08
03/17/92	4	AMENDMENT	Patient # 008-022	129	4.08
03/17/92	4	AMENDMENT	Patient # 009-001	129	4.08
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	130	4.07
03/17/92	4	AMENDMENT	Patient # 007-007	130	4.07

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Patient # 021-005	123	4.14
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	124	4.15
03/17/92	4	AMENDMENT	Patient # 013-005	124	4.15
03/17/92	4	AMENDMENT	Patient # 015-006	124	4.15
03/17/92	4	AMENDMENT	Patient # 015-008	124	4.15
03/17/92	4	AMENDMENT	Patient # 015-015	124	4.15
03/17/92	4	AMENDMENT	Patient # 019-006	124	4.15
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	125	4.12
03/17/92	4	AMENDMENT	Patient # 009-082	125	4.12
03/17/92	4	AMENDMENT	Patient # 009-089	125	4.12
03/17/92	4	AMENDMENT	Patient # 012-001	125	4.12
03/17/92	4	AMENDMENT	Patient # 012-005	125	4.12
03/17/92	4	AMENDMENT	Patient # 013-004	125	4.12
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	126	4.11
03/17/92	4	AMENDMENT	Patient # 009-048	126	4.11
03/17/92	4	AMENDMENT	Patient # 009-067	126	4.11
03/17/92	4	AMENDMENT	Patient # 009-071	126	4.11
03/17/92	4	AMENDMENT	Patient # 009-073	126	4.11

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	121	4.16
03/17/92	4	AMENDMENT	Patient # 028-006	121	4.16
03/17/92	4	AMENDMENT	Patient # 028-008	121	4.16
03/17/92	4	AMENDMENT	Patient # 028-010	121	4.16
03/17/92	4	AMENDMENT	Patient # 037-004	121	4.16
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	122	4.15
03/17/92	4	AMENDMENT	Patient # 021-017	122	4.15
03/17/92	4	AMENDMENT	Patient # 023-001	122	4.15
03/17/92	4	AMENDMENT	Patient # 023-028	122	4.15
03/17/92	4	AMENDMENT	Patient # 023-029	122	4.15
03/17/92	4	AMENDMENT	Patient # 023-031	122	4.15
03/17/92	4	AMENDMENT	Patient # 023-035	122	4.15
03/17/92	4	AMENDMENT	Patient # 024-005	122	4.15
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	123	4.14
03/17/92	4	AMENDMENT	Patient # 019-013	123	4.14
03/17/92	4	AMENDMENT	Patient # 019-019	123	4.14
03/17/92	4	AMENDMENT	Patient # 020-004	123	4.14
03/17/92	4	AMENDMENT	Patient # 020-012	123	4.14

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
3/17/92	4	AMENDMENT	Patient # 007-024	118	4.19
3/17/92	4	AMENDMENT	Patient # 007-025	118	4.19
3/17/92	4	AMENDMENT	Patient # 008-002	118	4.19
3/17/92	4	AMENDMENT	Patient # 009-003	118	4.19
3/17/92	4	AMENDMENT	Case Report Forms - CS# 087027	119	4.18
3/17/92	4	AMENDMENT	Patient # 001-005	119	4.18
3/17/92	4	AMENDMENT	Patient # 001-007	119	4.18
3/17/92	4	AMENDMENT	Patient # 001-010	119	4.18
3/17/92	4	AMENDMENT	Patient # 004-005	119	4.18
3/17/92	4	AMENDMENT	Patient # 004-006	119	4.18
3/17/92	4	AMENDMENT	Patient # 004-020	119	4.18
3/17/92	4	AMENDMENT	Case Report Forms - CS# 087023 (Continued)	120	4.17
3/17/92	4	AMENDMENT	Patient # 038-022	120	4.17
3/17/92	4	AMENDMENT	Patient # 038-027	120	4.17
3/17/92	4	AMENDMENT	Patient # 042-010	120	4.17
3/17/92	4	AMENDMENT	Patient # 042-011	120	4.17
3/17/92	4	AMENDMENT	Patient # 046-002	120	4.17
3/17/92	4	AMENDMENT	Patient # 046-011	120	4.17

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
3/17/92	4	AMENDMENT	Patient # 016-002	115	4.22
3/17/92	4	AMENDMENT	Patient # 018-001	115	4.22
3/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	116	4.21
3/17/92	4	AMENDMENT	Patient # 009-041	116	4.21
3/17/92	4	AMENDMENT	Patient # 010-004	116	4.21
3/17/92	4	AMENDMENT	Patient # 010-008	116	4.21
3/17/92	4	AMENDMENT	Patient # 010-012	116	4.21
3/17/92	4	AMENDMENT	Patient # 010-013	116	4.21
3/17/92	4	AMENDMENT	Patient # 010-025	116	4.21
3/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	117	4.20
3/17/92	4	AMENDMENT	Patient # 009-013	117	4.20
3/17/92	4	AMENDMENT	Patient # 009-014	117	4.20
3/17/92	4	AMENDMENT	Patient # 009-018	117	4.20
3/17/92	4	AMENDMENT	Patient # 009-025	117	4.20
3/17/92	4	AMENDMENT	Patient # 009-028	117	4.20
3/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	118	4.19
3/17/92	4	AMENDMENT	Patient # 007-006	118	4.19
3/17/92	4	AMENDMENT	Patient # 007-014	118	4.19

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Patient # 023-012	112	4.25
03/17/92	4	AMENDMENT	Patient # 023-015	112	4.25
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	113	4.24
03/17/92	4	AMENDMENT	Patient # 020-009	113	4.24
03/17/92	4	AMENDMENT	Patient # 020-010	113	4.24
03/17/92	4	AMENDMENT	Patient # 023-003	113	4.24
03/17/92	4	AMENDMENT	Patient # 023-004	113	4.24
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	114	4.23
03/17/92	4	AMENDMENT	Patient # 018-004	114	4.23
03/17/92	4	AMENDMENT	Patient # 018-005	114	4.23
03/17/92	4	AMENDMENT	Patient # 018-010	114	4.23
03/17/92	4	AMENDMENT	Patient # 018-011	114	4.23
03/17/92	4	AMENDMENT	Patient # 019-002	114	4.23
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	115	4.22
03/17/92	4	AMENDMENT	Patient # 012-001	115	4.22
03/17/92	4	AMENDMENT	Patient # 012-004	115	4.22
03/17/92	4	AMENDMENT	Patient # 012-014	115	4.22
03/17/92	4	AMENDMENT	Patient # 012-022	115	4.22

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
03/17/92	4	AMENDMENT	Patient # 032-001	109	4.28
03/17/92	4	AMENDMENT	Patient # 032-003	109	4.28
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	110	4.27
03/17/92	4	AMENDMENT	Patient # 028-004	110	4.27
03/17/92	4	AMENDMENT	Patient # 028-007	110	4.27
03/17/92	4	AMENDMENT	Patient # 028-008	110	4.27
03/17/92	4	AMENDMENT	Patient # 028-010	110	4.27
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	111	4.26
03/17/92	4	AMENDMENT	Patient # 023-022	111	4.26
03/17/92	4	AMENDMENT	Patient # 023-024	111	4.26
03/17/92	4	AMENDMENT	Patient # 024-004	111	4.26
03/17/92	4	AMENDMENT	Patient # 024-016	111	4.26
03/17/92	4	AMENDMENT	Patient # 025-007	111	4.26
03/17/92	4	AMENDMENT	Patient # 026-001	111	4.26
03/17/92	4	AMENDMENT	Patient # 028-001	111	4.26
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	112	4.25
03/17/92	4	AMENDMENT	Patient # 023-007	112	4.25
03/17/92	4	AMENDMENT	Patient # 023-010	112	4.25

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03/17/92	4	AMENDMENT	Patient # 503-028	106	4.31
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	107	4.30
03/17/92	4	AMENDMENT	Patient # 501-006	107	4.30
03/17/92	4	AMENDMENT	Patient # 503-001	107	4.30
03/17/92	4	AMENDMENT	Patient # 503-002	107	4.30
03/17/92	4	AMENDMENT	Patient # 503-011	107	4.30
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	108	4.29
03/17/92	4	AMENDMENT	Patient # 033-001	108	4.29
3/17/92	4	AMENDMENT	Patient # 033-005	108	4.29
3/17/92	4	AMENDMENT	Patient # 035-001	108	4.29
3/17/92	4	AMENDMENT	Patient # 037-003	108	4.29
3/17/92	4	AMENDMENT	Patient # 038-003	108	4.29
3/17/92	4	AMENDMENT	Patient # 501-002	108	4.29
3/17/92	4	AMENDMENT	Patient # 501-004	108	4.29
3/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	109	4.28
3/17/92	4	AMENDMENT	Patient # 028-011	109	4.28
3/17/92	4	AMENDMENT	Patient # 029-001	109	4.28
3/17/92	4	AMENDMENT	Patient # 031-002	109	4.28

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03/09/92		FDA LETTER	Requesting Additional Clinical Data (Revised Data Files)	103	N/A
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	104	4.33
03/17/92	4	AMENDMENT	Patient # 505-007	104	4.33
03/17/92	4	AMENDMENT	Patient # 511-004	104	4.33
03/17/92	4	AMENDMENT	Patient # 512-005	104	4.33
03/17/92	4	AMENDMENT	Patient # 512-008	104	4.33
03/17/92	4	AMENDMENT	Patient # 512-011	104	4.33
03/17/92	4	AMENDMENT	Patient # 512-014	104	4.33
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	105	4.32
03/17/92	4	AMENDMENT	Patient # 503-029	105	4.32
03/17/92	4	AMENDMENT	Patient # 503-038	105	4.32
03/17/92	4	AMENDMENT	Patient # 503-039	105	4.32
03/17/92	4	AMENDMENT	Patient # 503-043	105	4.32
03/17/92	4	AMENDMENT	Patient # 504-003	105	4.32
03/17/92	4	AMENDMENT	Case Report Forms - CS# 087027 (Continued)	106	4.31
03/17/92	4	AMENDMENT	Patient # 503-012	106	4.31
03/17/92	4	AMENDMENT	Patient # 503-016	106	4.31
03/17/92	4	AMENDMENT	Patient # 503-022	106	4.31

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01/16/92	3	ORIGINAL SUBMISSION	Cover Letter	103	3.01
01/16/92	3	ORIGINAL SUBMISSION	FDA Form 356H	103	3.01
01/16/92	3	ORIGINAL SUBMISSION	Letters of Authorization	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Patent Information	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	INDEX	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	GLOBAL SUMMARY	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Index to Section	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Annotated Labeling	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Pharmacologic Class, Scientific Rationale, Intended Use, Potential Clinical Benefits	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Foreign Marketing History	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Human Pharmacokinetics and Bioavailability summary	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Microbiology Summary	103	3.01
1/16/92	3	ORIGINAL SUBMISSION	Benefit/Risk Assessment and Proposed Post-Marketing Studies	103	3.01
1/24/92		FDA LETTER	Acknowledgement of Receipt	103	N/A

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 606i	101	3.03
01/16/92	3	ORIGINAL SUBMISSION	Report No. 607i	101	3.03
01/16/92	3	ORIGINAL SUBMISSION	Pharmacokinetics Individual Reports - Bioavailability/Bioequivalence Studies	101	3.03
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i	101	3.03
01/16/92	3	ORIGINAL SUBMISSION	CHEMISTRY, MANUFACTURING AND CONTROLS	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Environmental Assessment	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	SAMPLES, METHODS VALIDATION AND LABELING	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Index to Section	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Samples (four identical sets to be submitted at FDA's Request	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Methods Validation Package	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Samples and Supporting Documentation	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Proposed Regulatory Specifications (X-ref. to NDA page where located)	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Reference Standard	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Methods of Analysis	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Supporting Data	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Results of Tests	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Material Safety Data Sheets	102	3.02
01/16/92	3	ORIGINAL SUBMISSION	Labeling	102	3.02

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 610i	95	3.09
01/16/92	3	ORIGINAL SUBMISSION	Report No. 612i, Part II	96	3.08
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i (cont.)	97	3.07
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i (cont.)	98	3.06
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i (cont.)	99	3.05
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i (cont.)	100	3.04
01/16/92	3	ORIGINAL SUBMISSION	HUMAN PHARMACOKINETICS AND BIOAVAILABILITY	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Overview	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	References	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Summary Tables	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Summary Table of Pharmacokinetic Studies	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Summary Table of In Vivo Kinetic Data	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Summary Table of Analytical Methods	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Pharmacokinetics Individual Reports - Pilot Studies	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Report No. 605i	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Report No. 608i	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Report No. 608i	101	3.03
1/16/92	3	ORIGINAL SUBMISSION	Report No. 603i	101	3.03

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 622i (cont.)	82	3.22
01/16/92	3	ORIGINAL SUBMISSION	Report No. 622i	83	3.21
01/16/92	3	ORIGINAL SUBMISSION	Report No. 087039-000 (cont.)	84	3.20
01/16/92	3	ORIGINAL SUBMISSION	Report No. 087039-000	85	3.19
01/16/92	3	ORIGINAL SUBMISSION	Report No. 616i (cont.)	86	3.18
01/16/92	3	ORIGINAL SUBMISSION	Report No. 616i	87	3.17
01/16/92	3	ORIGINAL SUBMISSION	Report No. 615i	88	3.16
01/16/92	3	ORIGINAL SUBMISSION	Report No. 614i (cont.)	89	3.15
01/16/92	3	ORIGINAL SUBMISSION	Report No. 614i	90	3.14
01/16/92	3	ORIGINAL SUBMISSION	Report No. 621i (cont.)	91	3.13
01/16/92	3	ORIGINAL SUBMISSION	Report No. 621i	92	3.12
01/16/92	3	ORIGINAL SUBMISSION	Report No. 613i (cont.)	93	3.11
01/16/92	3	ORIGINAL SUBMISSION	Report No. 609i	94	3.10
01/16/92	3	ORIGINAL SUBMISSION	Pharmacokinetic Individual Reports - Selected Populations	94	3.10
01/16/92	3	ORIGINAL SUBMISSION	Report No. 613i	94	3.10
01/16/92	3	ORIGINAL SUBMISSION	Pharmacokinetics Individual Reports - Pharmacokinetic Studies	95	3.09
01/16/92	3	ORIGINAL SUBMISSION	Report No. 617i	95	3.09
01/16/92	3	ORIGINAL SUBMISSION	Report No. 618i	95	3.09

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 213i	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. 814i	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. 620i	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Other In Vitro Studies	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. 806i	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. 813i	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Pharmacokinetic Individual Reports - Validated Bioanalytical Methodologies	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. 131i	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. 807i	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. 132i	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. 811i	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Published Literature - Bibliography References	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0117	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0083	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0002	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0049	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0171	81	3.23
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0230	81	3.23

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 087039	78	3.26
01/16/92	3	ORIGINAL SUBMISSION	Report No. 817i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	Report No. 815i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	Report No. 802i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	Report No. 809i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	Report No. 810i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	Report No. 804i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	Report No. 609i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	Report No. 618i	79	3.25
01/16/92	3	ORIGINAL SUBMISSION	MICROBIOLOGY	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Summary	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Individual Reports	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0016	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0024	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0198	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0141	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. 211i	80	3.24
01/16/92	3	ORIGINAL SUBMISSION	Report No. 212i	80	3.24

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i (cont.)	71	3.33
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i (cont.)	72	3.32
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i (cont.	73	3.31
01/16/92	3	ORIGINAL SUBMISSION	Report No. 623i	74	3.30
01/16/92	3	ORIGINAL SUBMISSION	Report No. 622i	75	3.29
01/16/92	3	ORIGINAL SUBMISSION	Report No. 811i	76	3.28
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0053	76	3.28
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0207	76	3.28
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0184	76	3.28
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0208	76	3.28
01/16/92	3	ORIGINAL SUBMISSION	Report No. 610i	76	3.28
01/16/92	3	ORIGINAL SUBMISSION	Report No. 087039 (cont.)	77	3.27
01/16/92	3	ORIGINAL SUBMISSION	Report No. 813i	78	3.26
01/16/92	3	ORIGINAL SUBMISSION	Report No. 608i	78	3.26
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0049	78	3.26
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0006	78	3.26
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0054	78	3.26
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0095	78	3.26

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01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0090	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0223	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0104	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0048	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0299A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0327A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0188	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0086	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0323A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0438A	65	3.39
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0441A	65	3.39
01/16/92	3	ORIGINAL SUBMISSION	Report No. 614i	66	3.38
01/16/92	3	ORIGINAL SUBMISSION	Report No. 621i	67	3.37
01/16/92	3	ORIGINAL SUBMISSION	Report No. 616i	68	3.36
01/16/92	3	ORIGINAL SUBMISSION	Report No. 613i (cont.)	69	3.35
01/16/92	3	ORIGINAL SUBMISSION	Report No. 617i	70	3.34
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0128	70	3.34
01/16/92	3	ORIGINAL SUBMISSION	Report No. 613i	70	3.34

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01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0118	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0334A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. 218i	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0023	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0348A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0326A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0175	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0099	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0190	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0386A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0161	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0123	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0295A	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0142	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0189	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0138	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. 087021	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0073	64	3.40

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 223i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 620i	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0033	64	3.40
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0296A	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0121	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0156	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0039	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0004	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0004	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0302A	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0078	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0124	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. Ax0135	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0038	64	3.40
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0034	64	3.40
/16/92	3	ORIGINAL SUBMISSION	Report No. Ax0133	64	3.40
/16/92	3	ORIGINAL SUBMISSION	Report No. AX0180	64	3.40
/16/92	3	ORIGINAL SUBMISSION	Report No. AX0331A	64	3.40

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01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0170	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 201i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0001	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0085	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0074	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0035	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0056	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0132	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 208i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0132	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 208i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 216i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report NO. AX0096	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0173	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0164	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0149	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0336A	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. PH-001	63	3.41

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 204i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 206i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 214i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0089	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0019	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0072	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0122	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0071	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0010	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0092	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. 209i	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0186	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0226	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0182	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0221	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0181	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0057	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0169	63	3.41

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01/16/92	3	ORIGINAL SUBMISSION	Report No. 723i (cont.)	58	3.46
01/16/92	3	ORIGINAL SUBMISSION	Report No. 723i (cont.)	59	3.45
01/16/92	3	ORIGINAL SUBMISSION	Report No. 723i (cont.)	60	3.44
01/16/92	3	ORIGINAL SUBMISSION	Report No. 723i (cont.)	61	3.43
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0111	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0148	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0108	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0064	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0046	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. 221i	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. 217i	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. 219i	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0432A	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. 723i	62	3.42
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0130	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0134	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0382A	63	3.41
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0209	63	3.41

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01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0190A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0211A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0140A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0224A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0268A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0059	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0226A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0235A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0182A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0273A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0154	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0187	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0140	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0321A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0055	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0220	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0315A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0215A	57	3.47

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01/16/92	3	ORIGINAL SUBMISSION	CLINICAL DATA	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Index to Section	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	List of Investigators, List of INDs and NDAs	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	List of Investigators	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	List of Clinical Studies	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	List of INDs	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Background/Overview of Clinical Investigations	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Individual Reports	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0363A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0282A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0200	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0125A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0360A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0185A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0361A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0134A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0254A	56	3.48
01/16/92	3	ORIGINAL SUBMISSION	Report No. AX0109A	56	3.48

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01/16/92	3	ORIGINAL SUBMISSION	CS# 087027 (cont.)	46	3.58
01/16/92	3	ORIGINAL SUBMISSION	CS# 087027 (cont.)	47	3.57
01/16/92	3	ORIGINAL SUBMISSION	CS# 087027 (cont.)	48	3.56
01/16/92	3	ORIGINAL SUBMISSION	CS# 087027	49	3.55
01/16/92	3	ORIGINAL SUBMISSION	CS# 087023 (cont.)	50	3.54
01/16/92	3	ORIGINAL SUBMISSION	CS# 087023 (cont.)	51	3.53
01/16/92	3	ORIGINAL SUBMISSION	CS# 087023 (cont.)	52	3.52
01/16/92	3	ORIGINAL SUBMISSION	CONTROLLED CLINICAL STUDIES	53	3.51
01/16/92	3	ORIGINAL SUBMISSION	Table of All Studies	53	3.51
01/16/92	3	ORIGINAL SUBMISSION	CS# 087023	53	3.51
01/16/92	3	ORIGINAL SUBMISSION	Report No. 619i	54	3.50
01/16/92	3	ORIGINAL SUBMISSION	CLINICAL PHARMACOLOGY	55	3.49
01/16/92	3	ORIGINAL SUBMISSION	Summary Tables	55	3.49
01/16/92	3	ORIGINAL SUBMISSION	Individual Study Summaries	55	3.49
01/16/92	3	ORIGINAL SUBMISSION	Overall Summary of Clinical Pharmacology	55	3.49
01/16/92	3	ORIGINAL SUBMISSION	Individual Reports	55	3.49
01/16/92	3	ORIGINAL SUBMISSION	Report No. 614i - See Volume 3.14		
01/16/92	3	ORIGINAL SUBMISSION	Report No. 611i	55	3.49

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01/16/92	3	ORIGINAL SUBMISSION	CS# AR86601 (708i) - See IND 29,607 Serial No. 156	155*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# BR86601 (706i) - See IND 29,607 Serial No. 156	153*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# IT86604 (713i) - See IND 29,607 Serial No. 156	147*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# IT86601 (712i) - See IND 29,607 Serial No. 156	146*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# ES86602 (714i) - See IND 29,607 Serial No. 156	149*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# TH86601 (715i) - See IND 29,607 Serial No. 156	151*	IND
1/16/92	3	ORIGINAL SUBMISSION	Individual Reports - CHRONIC RESISTANT TUBERCULOSIS, Domestic Uncontrolled	134*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# 087044 (722i) - See IND 29,607 Serial No. 156	134*	IND
1/16/92	3	ORIGINAL SUBMISSION	Individual Reports - CHRONIC RESISTANT TUBERCULOSIS, Foreign Uncontrolled	137*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# DZ87601 (709i) - See IND 29,607 Serial No. 156	137*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# AR86606 (710i) - See IND 29,607 Serial No. 156	139*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# FR86601 (717i) - See IND 29, 607 Serial No. 156	136*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# ES86601 (711i) - See IND 29, 607 Serial No. 156	138*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# ZA86603 (716i) - See IND 29,607 Serial No. 156	135*	IND
1/16/92	3	ORIGINAL SUBMISSION	Individual Reports - CROHN'S DISEASE, Domestic Uncontrolled	110*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# 087004/087008 - Summary Only - See IND 29,607 Serial No. 156	110*	IND
/16/92	3	ORIGINAL SUBMISSION	Individual Reports - LEPROSY, Domestic Uncontrolled	110*	IND
/16/92	3	ORIGINAL SUBMISSION	CS# 087007 - Summary Only - See IND 29,607 Serial No. 156	110*	IND

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01/16/92	3	ORIGINAL SUBMISSION	CS# 087065	45	3.59
01/16/92	3	ORIGINAL SUBMISSION	Individual Reports - MAC TREATMENT, AIDS, Domestic Uncontrolled	45	3.59
01/16/92	3	ORIGINAL SUBMISSION	CS# 087042 (723i) - See IND 29,607 Serial No. 156	122*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# 087033 (720i) - See IND 29,607 Serial No. 156	127*	IND
01/16/92	3	ORIGINAL SUBMISSION	Individual Reports - MAC TREATMENT, AIDS, Foreign Uncontrolled	129*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# 087041 (724i) - See IND 29,607 Serial No. 156	129*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# 087053, FR86603 (718i) - See IND 29,607 Serial No. 156	130*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# 087054 (721i) - See IND 29,607 Serial No. 156	128*	IND
01/16/92	3	ORIGINAL SUBMISSION	Individual Reports - PULMONARY MAC, NON-AIDS, Domestic Controlled	130*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS# 087011 - Summary Only - See IND 29,607 Serial No. 156	130*	IND
01/16/92	3	ORIGINAL SUBMISSION	Individual Reports - PULMONARY MAC, NON-AIDS, Domestic Uncontrolled	116*	IND
01/16/92	3	ORIGINAL SUBMISSION	CS#087043 (719i) - See IND 29,607 Serial No. 156	116*	IND
1/16/92	3	ORIGINAL SUBMISSION	Individual Reports - PULMONARY MAC, NON-AIDS, Foreign Uncontrolled	117*	IND
1/16/92	3	ORIGINAL SUBMISSION	CS# FR86602 (707i) - See IND 29,607 Serial No. 156	117*	IND
1/16/92	3	ORIGINAL SUBMISSION	Individual Reports - ANTI-HIV ACTIVITY, Domestic Uncontrolled		
1/16/92	3	ORIGINAL SUBMISSION	CS# 087003 (619i) - See Volume 3.50		
1/16/92	3	ORIGINAL SUBMISSION	CS# 087005 (618i) - See Volume 3.09		
1/16/92	3	ORIGINAL SUBMISSION	Individual Reports - NEWLY DIAGNOSED TUBERCULOSIS, Foreign Controlled	155*	IND

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1/16/92	3	ORIGINAL SUBMISSION	INTEGRATED SUMMARY OF BENEFITS AND RISKS OF THE DRUG	44	3.60
1/16/92	3	ORIGINAL SUBMISSION	Commercial Marketing Experience	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	Overall Summary of Other Studies and Information	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	Published Literature Bibliography	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	OTHER STUDIES AND INFORMATION - A portion of this section was submitted to IND 29,607 on November 26, 1991	110*	IND
1/16/92	3	ORIGINAL SUBMISSION	Serial No. 156 and cross referenced to this NDA submission	110*	IND
1/16/92	3	ORIGINAL SUBMISSION	Table of Studies	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	Additional Experience on Safety of Rifabutin	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	Summary	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	Table of Studies	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	Publications	45	3.59
1/16/92	3	ORIGINAL SUBMISSION	Report No. AX0216	45	3.59
/16/92	3	ORIGINAL SUBMISSION	Report No. AX0219	45	3.59
/16/92	3	ORIGINAL SUBMISSION	Report No. AX0220	45	3.59
/16/92	3	ORIGINAL SUBMISSION	Report No. AX0136	45	3.59
/16/92	3	ORIGINAL SUBMISSION	Report No. AX0178	45	3.59
/16/92	3	ORIGINAL SUBMISSION	Report No. AX0116	45	3.59
/16/92	3	ORIGINAL SUBMISSION	Individual Reports - MAC TREATMENT, AIDS, Domestic Controlled	45	3.59

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01/16/92	3	ORIGINAL SUBMISSION	Integrated Summary of Effectiveness Data	35	3.69
01/16/92	3	ORIGINAL SUBMISSION	Integrated Summary of Safety Information	35	3.69
01/16/92	3	ORIGINAL SUBMISSION	Integrated Summary of Benefits and Risks	35	3.69
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies (cont.)	36	3.68
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies (cont.)	37	3.67
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies (cont.)	38	3.66
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies (cont.)	39	3.65
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies (cont.)	40	3.64
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies (cont.)	41	3.63
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies (cont.)	42	3.62
01/16/92	3	ORIGINAL SUBMISSION	STATISTICAL SECTION	43	3.61
01/16/92	3	ORIGINAL SUBMISSION	Index fo Section	43	3.61
01/16/92	3	ORIGINAL SUBMISSION	List of Investigators, List of INDs, and NDAs	43	3.61
01/16/92	3	ORIGINAL SUBMISSION	Background/Overview of Clinical Investigations	43	3.61
01/16/92	3	ORIGINAL SUBMISSION	Controlled Clinical Studies	43	3.61
01/16/92	3	ORIGINAL SUBMISSION	INTEGRATED SUMMARY OF EFFECTIVENESS DATA	44	3.60
01/16/92	3	ORIGINAL SUBMISSION	INTEGRATED SUMMARY OF SAFETY INFORMATION	44	3.60
01/16/92	3	ORIGINAL SUBMISSION	DRUG ABUSE AND OVERDOSAGE INFORMATION	44	3.60

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10/07/91	1	Original Submission	Report # 302i	1	1.27
10/07/91	1	Original Submission	Report # 309i	1	1.27
10/07/91	1	Original Submission	Report # 311i	1	1.27
10/07/91	1	Original Submission	REport # 312i	1	1.27
10/07/91	1	Original Submission	Report # 409i	2	1.26
10/07/91	1	Original Submission	Report # 425i	2	1.26
10/07/91	1	Original Submission	Toxicology Individual Reports - Mutagenicity	2	1.26
10/07/91	1	Original Submission	Report # 305i	2	1.26
10/07/91	1	Original Submission	Report # 306i	2	1.26
10/07/91	1	Original Submission	Report # 307i	2	1.26
10/07/91	1	Original Submission	Report # 308i	2	1.26
10/07/91	1	Original Submission	Report # 414i	3	1.25
10/07/91	1	Original Submission	Report # 412i	3	1.25
10/07/91	1	Original Submission	Report # 422i	4	1.24
10/07/91	1	Original Submission	Report # 429i	5	1.23
10/07/91	1	Original Submission	Report # 407i	5	1.23
10/07/91	1	Original Submission	Report # 423i	5	1.23
10/07/91	1	Original Submission	Toxicology Individual Reports - Special Studies	6	1.22

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10/07/91	1	Original Submission	Report # 310i	6	1.22
10/07/91	1	Original Submission	Report # 419i	6	1.22
10/07/91	1	Original Submission	Report # 433i (cont.)	7	1.21
10/07/91	1	Original Submission	Report # 433i (cont.)	8	1.20
10/07/91	1	Original Submission	Report # 433i (cont.)	9	1.19
10/07/91	1	Original Submission	Report # 433i	10	1.18
10/07/91	1	Original Submission	Report # 432i (cont.)	11	1.17
10/07/91	1	Original Submission	Report # 432i (cont.)	12	1.16
10/07/91	1	Original Submission	Report # 432i (cont.)	13	1.15
10/07/91	1	Original Submission	Report # 432i (cont.)	14	1.14
10/07/91	1	Original Submission	Toxicology Individual Reports - Carcinogenicity	15	1.13
10/07/91	1	Original Submission	Report # 432i	15	1.13
10/07/91	1	Original Submission	Report # 420i	16	1.12
10/07/91	1	Original Submission	Report # 424i	17	1.11
10/07/91	1	Original Submission	Toxicology Individual Reports - Chronic Toxicity	18	1.10
10/07/91	1	Original Submission	Report # 421i	18	1.10
10/07/91	1	Original Submission	Report # 402i	19	1.09
10/07/91	1	Original Submission	Report # 411i	19	1.09

MYCOBUTIN (Rifabutin) NDA 50-689

DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
10/07/91	1	Original Submission	Report # 418i	20	1.08
10/07/91	1	Original Submission	Report # 418i-Ai	20	1.08
10/07/91	1	Original Submission	Report # 431i	20	1.08
10/07/91	1	Original Submission	Report # 426i	21	1.07
10/07/91	1	Original Submission	Report # 408i	22	1.06
10/07/91	1	Original Submission	Report # 413i	22	1.06
10/07/91	1	Original Submission	Report # 403i	23	1.05
10/07/91	1	Original Submission	Report # 427i	24	1.04
10/07/91	1	Original Submission	Report # 405i	24	1.04
10/07/91	1	Original Submission	Report # 410i	25	1.03
10/07/91	1	Original Submission	Individual Reports - Acute Toxicity	26	1.02
10/07/91	1	Original Submission	Report # 401i	26	1.02
10/07/91	1	Original Submission	Report # 406i	26	1.02
10/07/91	1	Original Submission	Report # 417i	26	1.02
10/07/91	1	Original Submission	Report # 435i	26	1.02
10/07/91	1	Original Submission	Toxicolocy Individual Reports - Subchronic Toxicity	26	1.02
10/07/91	1	Original Submission	Report # 430i	26	1.02
10/07/91	1	Original Submission	Toxicology Expanded Table of Contents	27	1.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
10/07/91	1	Original Submission	Overview	27	1.01
10/07/91	1	Original Submission	Summary Tables	27	1.01
10/07/91	1	Original Submission	Individual Study Summaries	27	1.01
10/07/91	1	Original Submission	References	27	1.01
11/21/91	2	Original Submission	Enzyme Induction or Inhibition	28	2.07
11/21/91	2	Original Submission	Report No. 428i	28	2.07
11/21/91	2	Original Submission	Report No. 304i	28	2.07
11/21/91	2	Original Submission	Report No. 303i	28	2.07
11/21/91	2	Original Submission	Metabolism Characteristics and Metabolites	28	2.07
11/21/91	2	Original Submission	Report No. 821i	28	2.07
11/21/91	2	Original Submission	Report No. 812i	28	2.07
11/21/91	2	Original Submission	Report No. 801i	28	2.07
11/21/91	2	Original Submission	Report No. 816i	28	2.07
11/21/91	2	Original Submission	Plasma Levels During Carcinogenicity Levels	28	2.07
11/21/91	2	Original Submission	Report No. 819i	28	2.07
11/21/91	2	Original Submission	Report No. 820i	28	2.07
11/21/91	2	Original Submission	Bioanalytical Methodologies	28	2.07
11/21/91	2	Original Submission	Report No. 805i	28	2.07

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
11/21/91	2	Original Submission	Report No. 807i	28	2.07
11/21/91	2	Original Submission	Report No. 811i	28	2.07
11/21/91	2	Original Submission	Published Literature Bibliography	28	2.07
11/21/91	2	Original Submission	Report No. AX0213	28	2.07
11/21/91	2	Original Submission	Report No. AX0047	28	2.07
11/21/91	2	Original Submission	Report No. 609i	28	2.07
11/21/91	2	Original Submission	Report No. AX0021	28	2.07
11/21/91	2	Original Submission	INDIVIDUAL REPORTS	29	2.06
11/21/91	2	Original Submission	Oral Absorption and Plasma Kinetics	29	2.06
11/21/91	2	Original Submission	Report No. 802i	29	2.06
11/21/91	2	Original Submission	Report No. 814i	29	2.06
11/21/91	2	Original Submission	Report No. 817i	29	2.06
11/21/91	2	Original Submission	Report No. 802i	29	2.06
11/21/91	2	Original Submission	Report No. 809i	29	2.06
11/21/91	2	Original Submission	Report No. 815i	29	2.06
11/21/91	2	Original Submission	Report No. 803i	29	2.06
11/21/91	2	Original Submission	Plasma Protein Binding	29	2.06
11/21/91	2	Original Submission	Report No. 813i	29	2.06

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11/21/91	2	Original Submission	Report No. 806i	29	2.06
11/21/91	2	Original Submission	Tissue Distribution/Accumulation	29	2.06
11/21/91	2	Original Submission	Report No. 810i	29	2.06
11/21/91	2	Original Submission	Report No. 804	29	2.06
11/21/91	2	Original Submission	Report No. 808i	29	2.06
11/21/91	2	Original Submission	Report No. 818i	29	2.06
11/21/91	2	Original Submission	Absorption, Distribution, Metabolism, and Excretion Studies	30	2.06
11/21/91	2	Original Submission	TABLE OF CONTENTS	30	2.05
11/21/91	2	Original Submission	OVERVIEW	30	2.05
11/21/91	2	Original Submission	SUMMARY TABLES	30	2.05
11/21/91	2	Original Submission	INDIVIDUAL STUDY SUMMARIES	30	2.05
11/21/91	2	Original Submission	REFERENCES	30	2.05
11/21/91	2	Original Submission	Report No. 207i	31	2.04
11/21/91	2	Original Submission	Report No. 205i	31	2.04
11/21/91	2	Original Submission	Report No. 301i	31	2.04
11/21/91	2	Original Submission	Report No. 220i	31	2.04
11/21/91	2	Original Submission	Report No. AX0185	31	2.04
11/21/91	2	Original Submission	Report No. AX0097	31	2.04

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1/21/91	2	Original Submission	Report No. AX0094	31	2.04
1/21/91	2	Original Submission	Other Pharmacology Studies	31	2.04
1/21/91	2	Original Submission	Report No. AX0088	31	2.04
1/21/91	2	Original Submission	Report No. 217i	31	2.04
1/21/91	2	Original Submission	Report No. 087901	31	2.04
1/21/91	2	Original Submission	Detailed Reports	32	2.03
1/21/91	2	Original Submission	Primary Therapeutic Effects	32	2.03
1/21/91	2	Original Submission	Report No. AX-0118	32	2.03
1/21/91	2	Original Submission	Report No. AX0134	32	2.03
1/21/91	2	Original Submission	Report No. PH-003	32	2.03
1/21/91	2	Original Submission	Report No. 087021-000	32	2.03
1/21/91	2	Original Submission	Report No. AX0139	32	2.03
1/21/91	2	Original Submission	Report No. AX0087	32	2.03
1/21/91	2	Original Submission	Report No. AX0048	32	2.03
1/21/91	2	Original Submission	Report No. AX0183	32	2.03
1/21/91	2	Original Submission	Report No. AX0086	32	2.03
1/21/91	2	Original Submission	Report No. 201i	32	2.03
1/21/91	2	Original Submission	Report No. 204i	32	2.03

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11/21/91	2	Original Submission	Report No. 214i	32	2.03
11/21/91	2	Original Submission	Report No. 210i	32	2.03
11/21/91	2	Original Submission	Report No. AX0010	32	2.03
11/21/91	2	Original Submission	Report No. AX0001	32	2.03
11/21/91	2	Original Submission	Report No. AX0072	32	2.03
11/21/91	2	Original Submission	Report No. 209i	32	2.03
11/21/91	2	Original Submission	Report No. AX0063	32	2.03
11/21/91	2	Original Submission	Report No. AX0018	32	2.03
11/21/91	2	Original Submission	Report No. AX0077	32	2.03
11/21/91	2	Original Submission	Report No. AX0008	32	2.03
11/21/91	2	Original Submission	Report No. PH-002	32	2.03
11/21/91	2	Original Submission	Mechanism of Action	32	2.03
11/21/91	2	Original Submission	Report No. AX006	32	2.03
11/21/91	2	Original Submission	Report No. AX0024	32	2.03
11/21/91	2	Original Submission	Report No. AX0198	32	2.03
11/21/91	2	Original Submission	Report No. AX0141	32	2.03
11/21/91	2	Original Submission	Report No. 211i	32	2.03
11/21/91	2	Original Submission	Report No. 212i	32	2.03

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
11/21/91	2	Original Submission	Report No. 213i	32	2.03
11/21/91	2	Original Submission	Safety Pharmacology	32	2.03
11/21/91	2	Original Submission	Report No. 203i	32	2.03
11/21/91	2	Original Submission	Report No. 202i	32	2.03
11/21/91	2	Original Submission	Report No. 222i	32	2.03
11/21/91	2	Original Submission	PHARMACOLOGY - 5A	33	2.02
11/21/91	2	Original Submission	TABLE OF CONTENTS	33	2.02
1/21/91	2	Original Submission	OVERVIEW	33	2.02
1/21/91	2	Original Submission	SUMMARY TABLES	33	2.02
1/21/91	2	Original Submission	INDIVIDUAL STUDY SUMMARIES	33	2.02
1/21/91	2	Original Submission	REFERENCES	33	2.02
1/21/91	2	Original Submission	Cover Letter	34	2.01
1/21/91	2	Original Submission	Form FDA 1571	34	2.01
1/21/91	2	Original Submission	Index to 2nd NDA submission	34	2.01
1/21/91	2	Original Submission	SECTION 3 CHEMISTRY, MANUFACTURING AND CONTROLS	34	2.01
1/21/91	2	Original Submission	Expanded Table of Contents	34	2.01
1/21/91	2	Original Submission	Summary	34	2.01
1/21/91	2	Original Submission	Schematic	34	2.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
11/21/91	2	Original Submission	Description	34	2.01
11/21/91	2	Original Submission	Section 3A - Drug Substance	34	2.01
11/21/91	2	Original Submission	Batch Records	34	2.01
11/21/91	2	Original Submission	Attachment A - Master Batch Record (in Italian)	34	2.01
11/21/91	2	Original Submission	Attachment B - Master Batch Record (English translation)	34	2.01
1/21/91	2	Original Submission	Attachment C - Actual Batch Record	34	2.01
1/21/91	2	Original Submission	Description of Control Checks, Methods and Specifications during Synthesis	34	2.01
1/21/91	2	Original Submission	In-process Specifications and Methods	34	2.01
1/21/91	2	Original Submission	Step 1	34	2.01
1/21/91	2	Original Submission	Step 2	34	2.01
1/21/91	2	Original Submission	Step 3	34	2.01
1/21/91	2	Original Submission	Step 4	34	2.01
1/21/91	2	Original Submission	Related Substances	34	2.01
1/21/91	2	Original Submission	Shipping Container	34	2.01
1/21/91	2	Original Submission	Specifications and Analytical Methods	34	2.01
1/21/91	2	Original Submission	Specifications	34	2.01
1/21/91	2	Original Submission	Analytical Methods	34	2.01
1/21/91	2	Original Submission	Validation of Analytical Methods	34	2.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
11/21/91	2	Original Submission	Sampling, Testing and Release	34	2.01
11/21/91	2	Original Submission	Comparative Batch Analysis	34	2.01
11/21/91	2	Original Submission	Reference Standard	34	2.01
11/21/91	2	Original Submission	Synthesis	34	2.01
11/21/91	2	Original Submission	Characterization	34	2.01
11/21/91	2	Original Submission	Section 3B - Drug Product	34	2.01
11/21/91	2	Original Submission	Components	34	2.01
11/21/91	2	Original Submission	Active Ingredient	34	2.01
11/21/91	2	Original Submission	Inactive Ingredients	34	2.01
11/21/91	2	Original Submission	Composition	34	2.01
11/21/91	2	Original Submission	Quantitative Composition	34	2.01
11/21/91	2	Original Submission	DMF Letter of Authorization	34	2.01
11/21/91	2	Original Submission	Specifications and Analytical Methodsfor Inactive Compounds	34	2.01
11/21/91	2	Original Submission	Specifications	34	2.01
11/21/91	2	Original Submission	Methods	34	2.01
11/21/91	2	Original Submission	Name and Address of Manufacturer(s)	34	2.01
11/21/91	2	Original Submission	Farmitalia Carlo Erba	34	2.01
11/21/91	2	Original Submission	DMF Letter of Authorization	34	2.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
11/21/91	2	Original Submission	Adria Laboratories	34	2.01
11/21/91	2	Original Submission	Packaging Coordinators	34	2.01
11/21/91	2	Original Submission	DMF Letter of Authorization	34	2.01
11/21/91	2	Original Submission	Method(s) of Manufacture and Packaging	34	2.01
11/21/91	2	Original Submission	Manufacturing Procedure	34	2.01
11/21/91	2	Original Submission	In-process Controls	34	2.01
11/21/91	2	Original Submission	Reprocessing Operations	34	2.01
11/21/91	2	Original Submission	Schematic Diagram	34	2.01
11/21/91	2	Original Submission	Batch Records	34	2.01
11/21/91	2	Original Submission	Attachment D - Actual Batch Record (in Italian)	34	2.01
11/21/91	2	Original Submission	Attachment E - Actual Batch Record (English Translation)	34	2.01
11/21/91	2	Original Submission	Packaging Components	34	2.01
11/21/91	2	Original Submission	Section 3B - Drug Product	34	2.01
11/21/91	2	Original Submission	Specifications and Analytical Methods for Drug Product	34	2.01
11/21/91	2	Original Submission	Specifications	34	2.01
11/21/91	2	Original Submission	Methods	34	2.01
11/21/91	2	Original Submission	Identification (UV)	34	2.01
11/21/91	2	Original Submission	Identification, Potency and Related Substances (HPLC)	34	2.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
11/21/91	2	Original Submission	HPLC Method Validation	34	2.01
11/21/91	2	Original Submission	Dissolution	34	2.01
11/21/91	2	Original Submission	Dissolution Validation	34	2.01
11/21/91	2	Original Submission	Finished Product Sampling	34	2.01
1/21/91	2	Original Submission	Finished Product Testing	34	2.01
1/21/91	2	Original Submission	Stability	34	2.01
1/21/91	2	Original Submission	Primary Stability Studies	34	2.01
1/21/91	2	Original Submission	General Product Information	34	2.01
1/21/91	2	Original Submission	Stability Specifications and Test Methodology	34	2.01
1/21/91	2	Original Submission	Study Design and Conditions	34	2.01
1/21/91	2	Original Submission	Stability Data Information	34	2.01
1/21/91	2	Original Submission	Supportive Stability Studies	34	2.01
1/21/91	2	Original Submission	Data Analysis and Conclusion	34	2.01
1/21/91	2	Original Submission	Stability Commitment & Protocol	34	2.01
1/21/91	2	Original Submission	Section 3C - Investigational Formulations	34	2.01
1/21/91	2	Original Submission	Formulations used in Clinical Studies	34	2.01
1/21/91	2	Original Submission	Current Formulation	34	2.01
1/21/91	2	Original Submission	Previous Formulation	34	2.01

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DATE	#	TYPE	LETTER SUBJECT	DRA VOL #	FDA VOL #
1/21/91	2	Original Submission	Oral Solution Formulation	34	2.01
1/21/91	2	Original Submission	Formulation Compositions	34	2.01

GRUPPO MONTEDISON

FARMITALIA CARLO ERBA

VIA CARLO IMBONATI, 24
20159 MILANO

TELEFONO (02) 6995 1 (CENTRALINO)
TELEGRAMMI ERBACAR-MILANO
CASELLA POSTALE 10512
C.C. POSTALE 619205
TELEX 330314 ERBA I

DATA 6th March 1986

VS RIF

NS RIF

TEL DIRETTO

Commissioner
Food and Drug Administration
Department of Health and
Human Services
5600 Fishers Lane
Rockville, MD 20857
U.S.A.

Gentlemen:

We, hereby, appoint Adria Laboratories, Division of Erbamont Inc., 5000 Post Road, Dublin, Ohio 43017 (Mailing Address: P.O. Box 16529, Columbus, Ohio 43216) as our lawful U.S. agent and representative in a decision making capacity concerning our drug master file (DMF) for rifabutin (Code: LM 427) capsules and active drug substances and any and all other regulatory activities that Farmitalia Carlo Erba S.p.A. may initiate with FDA concerning this product.

As our U.S. agent, Adria Laboratories will serve as a liaison and contact concerning all communications and activities with regard to the above DMF.

Communications and correspondence should be directed to the attention of: Director, Drug Regulatory Affairs.

Very truly yours,
FARMITALIA CARLO ERBA S.p.A.

Alberto Mario Ferrari
President

c.c.: Adria Laboratories
Erbamont Inc.

ADRIA LABORATORIES

ADMINISTRATIVE OFFICES:
ADRIA LABORATORIES
Division of Erbamont Inc
5000 Post Road, Dublin, Ohio
(614) 764-8100 Telex 246-620
Facsimile (614) 764-8102

April 16, 1986

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Edward Tabor, M.D.
Director
Division of Anti-infective Drug
Products (HFN-815)
Attention: Document Control Rm (12B-30)
Office of Biologics Research & Review
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IND 27,934
Rifabutin

Dear Dr. Tabor:

In reference to the above IND, we are enclosing for your information a letter from Farmitalia Carlo Erba, holder of DMF 4882 (rifabutin manufacturing and controls), appointing Adria Laboratories as their U.S. agent for the rifabutin DMF.

In the future, all communications and correspondence concerning the DMF should be directed to Adria Laboratories, attention: Director Drug Regulatory Affairs.

Sincerely yours,

Lowell Irminger

Lowell L. Irminger
Director Drug Regulatory Affairs

LLI/bd
enclosure

bcc: DMF
IND
FICE (G. Tabusso)
FICE (S. Duncan)
B. Ring
V. Fojas
E. Benjamin/F. Grab
DMF (FDA/C)
IND (FDA/C)